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A FORMULATION & EVALUATION OF MUCOADHESIVE BENZOCAINE GEL

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ABSTRACT
Gel dosage forms are successfully used as drug delivery systems considering their ability to control drug release and to protect medicaments from a hostile environment. The aim of this work was to investigate the properties of carbopol 934, HPMC K4M polymeric system in water-miscible co-solvents such as glycerin and alcohol. Benzocaine is a local anesthetic, treatment of mouth ulcer and mucosal pain relief. The mucosal gel formulation is applied in the treatment of dental pain Samples were prepared by simply dispersing different amounts of Carbopols (0.2-0.4%) into the alcoholic solution at the room temperature and were keep at 27,30 and 31°C. All these systems were then characterized for distribution, bio adhesiveness on the mucosa, physical stability and drug release. The Franz diffusion cell used to study in vitro drug release. The increase in carbopol concentration caused increased viscosity and bio adhesiveness. Neutralization of pH in various concentrations of carbopol gels showed resulted in increased viscosity. A relationship between the viscosity and bioadhesive strength was shown in the neutralized carbopol gels. On the other hand, the results indicated that increasing amount of carbopol 934,HPMC K4M and glycerine reduced drug release.

KEYWORDS: Benzocaine, Carbopol934, HPMC K4M, Glycerin, Ethanol, Camphor.

INTRODUCTION

INTRODUCTION OF GEL

The word "gel" is derived from "gelatin" & both "gel" & "jelly'" Can be traced back to the Latin gele for "frost" & gelare, meaning freeze or congeal. This origin indicates the essential idea of liquid setting to a solid like material that does not flow, but is elastic & retains liquid characteristics. The difference between gel & jelly remains somewhat arbitrary, with some differences based on the field of applications.

The gels as semisolid system consisting of either suspension made up of small inorganic particles or large molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles the gel is classified as two –phase system.

Single- phase gels consists of organic macromolecules uniformly distributed throughout a liquid in such a manner in that no apparent boundaries between the dispersed macromolecules and the liquid. Single phase gels and jellies can be described As three dimensional networks formed by adding macromolecules such as proteins, polysaccharides, and synthetic macro molecules to appropriate liquids. In pharmaceuticals applications, water and hydro alcoholic solutions are common many polymer gels exhibit reversibility between the gel state and sol, which is the fluid phase containing the dispersed or dissolved macromolecules.

However, formation of some polymer gels is irreversible because their chains are covalently bonded. The three dimensional networks formed in two phases gels in and jellies is formed by several inorganic colloidal clays. Formation of these in organic gels is reversible. Gels are generally considered to be more rigid than jellies because gels consists of more covalent cross links, a higher density of physical bonds, or simply less liquid gel – forming polymers procedure materials that span a range of rigidities , beginning with a sol and increasing in rigidity to a mucilage, jelly, gel and hydro gel.

The physical properties of gels and jellies can be classified based on two groups. Transitional properties associated with gels and jellies can be classified based on two groups. Transitional properties and rheological properties, yield Point and rupture Spectrophotometric and thermal technique are used identify gel microstructures (physical junction zones) and their related transitional properties. For example, nuclear magnetic resonance (NMR) spectroscopy measures the structural and dynamic characteristics of the polymer just prior to aggregation and gel formation and circular dichroism (CD) spectroscopy measures the conformational changes of the polymer during network

formation. Mechanical techniques are used to determine rheological properties of gel. These techniques employ either small deformation measurements that yield viscoelastic parameters or large deformation measurements that generate complete stress strain profile, which include failure parameters.[1] The majority of gels are formed by the aggregation of colloidal sol properties, the solid or semisolid system so formed being interpenetrated by liquid. Gelatin of lyophilic sols gels formed by lypholic sols can be divided into two groups depending on the nature of the bond between the chains of the network of gel.

Type 1 are irreversibly system with a three dimensional network formed by covalent bond between the micromolicall.

Type 2 gel are heat reversibly, a transition from the sol to gel occurring on either heating or cooling. Poly solution, for example. Gel on cooling below a certain temperature referred to as the gel point because of their gelling properties poly are used as jellies for the application of drugs to the skin on the application gel dried rapidly leaving a plastic film with the drug in intimate contact with the skin.[2]

SOL-GEL TRANSITION (GEL POINT)

Gel is formed under the prevailing experimental condition; rather a sol is formed by the polymer and solvent. This concentration depends on polymer-polymer and polymer-solvent interactions, the hydrophilic – lipophilic character of the polymer, and the molecular weight and flexibility for the chain furthermore, polymers that require ions to from gels have crucial gelling concentration that depend on the concentration these additives and many other variables. Table 2 lists ranges Gel transition may be dependent on polymer on polymer concentration or Sol temperature Spectrophotometric methods, as mentioned previously are used to probe Sol-Gel transitions that depend on the critical gelling concentration. Thermal methods, including differential scanning Calorimetric are used to measure Sol transitions, or melting temperature, of thermo reversible gels. A relationship for estimating the heat of gelatin was derived by Aldridge and ferry in which the dependence of the Sol-Gel transition temperature on polymer concentration was considered.

The Critical gelling concentration is the concentration below which no macroscopic of minimal concentration for substance to gel in water.[3]

There are two thermal gel points associated with thermo reversible gel. Shift in temp may cause gel formulation at the setting point or gel liquefaction at the melting point. In addition that than set of identical cross linkages. Agars gels show temp hysteresis; the gel sets at about 40^0Cand temp hysteresis may occur in some gel in which the gel setting point is lower than the melting point. The hysteresis behaviour indicate that junction zone constitute a family of association melts at about 90^oC.[4]

A.PHYSICAL AGING

Most gels have structures that have not attained equilibrium; different preparative method and condition influence the gel state. The gel physically ages as it moves toward equilibrium, making the history of gel sample an important consideration when measuring physical properties. Aging reflects in gel microstructure, where non covalent crosslink and breaking and reforming. Furthermore, instabilities caused by the non equilibrium state arise in some polymer gels; two examples are retrograditation and sysnersis.

Retrograditation is the spontaneous reversion of a polymer solution to a gel on standing. Polyvinyl alcohol dissolved in water undergoes retrograditation. Where by the stereo regular chains form microcrystalline aggregates as the solution ages. Polyvinyl alcohol gels retrograde, forming crystalline domains. Amylase, which is the linear polysaccharide fraction of starch, underground retrogression, reducing the physical stability for solution and gels over time.[5]

Sysnersis is the process whereby liquid is liberated spontaneously from the gel matrix. This instability arises from the non equilibrium state of the gel established as it was or because of a change in external condition. Equilibrium, elastic contraction forces of polymer chains are usually balance by solvent swelling forces, resulting from an osmotic pressure differential with change in temperature, for example, the osmotic pressure shifts, causing an elastic contraction of polymer chains. The contractive response squeezes excess liquid out of the matrix. Agar and carrageen an are example of gels the exhibit sysnersis.[6]

B. RHEOLOGICAL PROPERTIES

Like the transitional physical properties of gel are not easily characterized because they depend strongly on the attributes of the polymer, history of the gel sample, and experimental conditions. Most often, the apparent viscosity or gel strength increases with an increase in the effective crosslink density of the gel or in the concentration and average molecular weight of the polymer. However, a rise in temperature may increase or decrease the apparent viscosity, depending on the molecular interaction between the polymer and solvent. In addition the direction of change in apparent viscosity may not be readily predictable when additives such as ions, none-electrolytes, solvents or non solvents, and other compatible polymers are mixed with a gel depending on their rheological properties, physically bonded gels can be divided into three groups; entanglement networks, strong gels, and weak gels Entanglement networks behave as dilute solution when diluted below their critical gelling concentration, whereas strong gels have stress-strain profiles that include rupture points. Example of polymers that from

entanglement network are guar gum and hylauric acid; strong are formed by agar, calcium alginate, gelatin and pectin Weak gels are also entanglement network, but they undergo specific molecular interaction that increase their strength. Therefore, the rheological properties of weak gels are intermediate between those of entanglement network and strong gels. Xanthus gum and carbomer are examples of polymer that from weak gels. Hyaluronic acid generally forms an entanglement network, but under specific condition it forms a weak gel.[7]

C.RIGIDITY

The modules of rigidity, or shear modulus, is defined as the ratio of shear stress to strain. It is a measure of a gels ability to resist deformation. The minimum rigidity for a strong gel to resist deformation under its own weight is equal to about gpl which is the acceleration due to gravity(g), density(p), and a linear dimension(1) of the sample. Therefore, the minimum rigidity is about 100Pa (10^3 dyne/cm) for a gel sample 1cm long.[8]

D.RUPTURE STRENGTH

Rupture strength is equal to the stress at which a strong gel ruptures or fails rather than undergoing further strain. The rupture strength is determined by large-deformation measurement on instruments such as the instron tester, where the tensile stress is is applied to the sample. however, strong gel samples can only be tested in tension if they can support their own weight (24), and most physically cross linked gels are relatively weak, making this type of test difficult.[9]

GEL-FORMING SUBSTANCES AND THEIR PHARMACEUTICAL USES

Gel-forming hydrophilic are typically used to prepare lipid-free semisolid dosage forms, including dental, dermatological, nasal, ophthalmic, rectal, and vaginal gels and jellies. Gel vehicles containing therapeutic agents are especially useful for application to mucous membranes and ulcerated or burned tissues because their high water content reduces irritancy. Furthermore, these hydrophilic gels are easily removed by gentle rinsing or natural flushing with body fluids, reducing the propensity for mechanical abrasion. The superior optical clarity of synthetic polymer gels, such as those composed of poloxamer and carbomer, has led to the current interest in developing therapeutic ophthalmic gels.

Unconventional routes of drug administration but using gels and jellies are also being explored. Thus, two nasal jellies were developed and marketed. The intranasal vitamin B-12 gel.Nascobal (Schwarz pharma), is used as adietary supplement. The gel base is composed of a hydrophilic cellulose derivative, the exact nature of which is not disclosed. However, the gel is apparently odorless and non-irritating and adheres well to the mucous membrane.[10]

1.2 COMPOSITION OF GELS

Consist of a solid Gels three-dimensional network that spans the volume of a liquid medium and ensures it through surface tension effects. This internal network structure may result from physical bonds (physical gels) or chemical bonds (chemical gels) as well as crystallites or other junctions that remain intact within the extending fluid. Virtually any fluids can be used as an extender including water (hydro gels), oil and air (aero gel). Both by weight and volume, gels are mostly fluid in composition and thus exhibit densities similar to those of their constituent Liquids Edible jelly is a common example of a hydro gel and has approximately the density of water.[11]

1.3 TYPES OF GELS

A) HYDROGELS

Hydrogel is a network of polymer chains that are hydrophilic found as a colloidal gel in which water is the dispersion medium. Hydro gels are highly absorbent (they can contain over 99.9% water) natural or synthetic polymers. Haydrogels also possess a degree of flexibility very similar to natural, due to significant water content. Common uses for hydro gels include:-

Currently a used as scaffolds in tissue engineering. When used as scaffolds, hydro gels may contain human cells to repair tissue. Hydro gels- coated walls have been used for cell culture Environmentally sensitive hydro gels which are also known as a ‘Smart Gels’ or ‘Intelligent Gels’. These hydro gels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change. As sustained release drug delivery system. Provide absorption, desloughing and debriding of necrotic and fibrotic tissue ibrotic tissue. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors, as well as in DDS.

Used in disposable diapers where they absorbs urine, or in sanitary napkins. Contact lenses (silicone hydro gels, polyacrylamides, polymacon). ECG and EEG medical electrodes using hydrogels composed of cross-linked polymers (polyethylene oxide polyAMPS and polyvinyl pyrrolidone) water gel explosives, rectal drug delivary and diagnosis, other less common uses include breast implants now used in glue. Granules for holding soil moisture in arid areas. Dressings for healing of burn or other hard-to-heal wounds. Wounds gels are for helping to create or maintain a moist environment. Reservoirs in excellent topical drug delivery; particularly ionic drugs, delivered by iontoporiasis (see ion exchange resin). Common ingredients are eg. Polyvinyl alcohol, sodium polyacrylat, acrylate polymers and copolymers with an abundance of hydrophilic groups. Natural hydrogel materials are being investigated for tissue engineering these materials include agarose, methylcellulose, hyaluronan and other naturally derived polymers.[12]

B) XEROGELS

A xerogel is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15-50%) and enormous surface area (150-900 m^2/g), along with a very small pore size (1-10nm). When solvent removal occurs under hypercritical conditions, the network does not shrink and a highly porous, low –density material known as an is produced. Heat treatment of xerogel at elevated temperature produces viscous sinterintering(shrinkage of the xerogel due to viscous flow) and effectively transforms the porous gel into a dense glass.

C) ORGANOGELS

An Organogel is a non-crystalline, non-glassy thermoreversible (thermoplastic) solid material composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network. The liquid can be, for example. an orgnic solvent, mineral oil or vegetable oil. The solubility and particle dimensions of the structuring characteristics for the elastic properties and firmness of the Organogel. Often these systems are based on self-assembly of the structurant molecules.

Organogel have potential for use in a number of applications, such as in pharmaceuticals, cosmetics, art conversation and food. An example of formation of an undesired thermoreversible network is the occurrence of wax crystallization in petroleum.[13]

INTRODUCTION BUCCAL DRUG DELIVERY

Buccal drug delivery is one of the novel drug delivery systems. It localized the delivery of drug to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease.[14] Buccal drug delivery also a safer mode of drug delivery system and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism.[15] The administration of drug through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism.[16] It is possible bypass of first pass effect and avoidance of pre-systemic elimination within the gastrointestinal tract. Buccal route is preferred the drugs having poor bioavailability because of high first pass metabolism.[17] Mucoadhesion is the phenomenon between two materials which are held together for prolong period of time by interfacial force. It is generally referred as mucoadhesion when interaction occurs between polymer and epithelial surface.[18, 19] Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets.[20] Some of the potential sites for attachment of any mucoadhesive system include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively.[21]

Oral mucosa[22, 23]

The total area of the oral cavity is $100cm^2$. One third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The main role of oral mucosa is protection of tissue underlying. Lipid based permeability barriers in epithelium layer protect the tissues from fluid loss and also from the attack of harmful environmental agents like microbial toxins, antigens, carcinogens, enzymes etc. Oral epithelium proliferation time is 5-6 days. Oral cavity is that area of mouth delineated by the 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).Oral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

FUNCTIONS OF ORAL CAVITY[24]

- It helps in chewing, mastication and mixing of food stuff.
- It is Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water
- To aid in speech and breathing process.

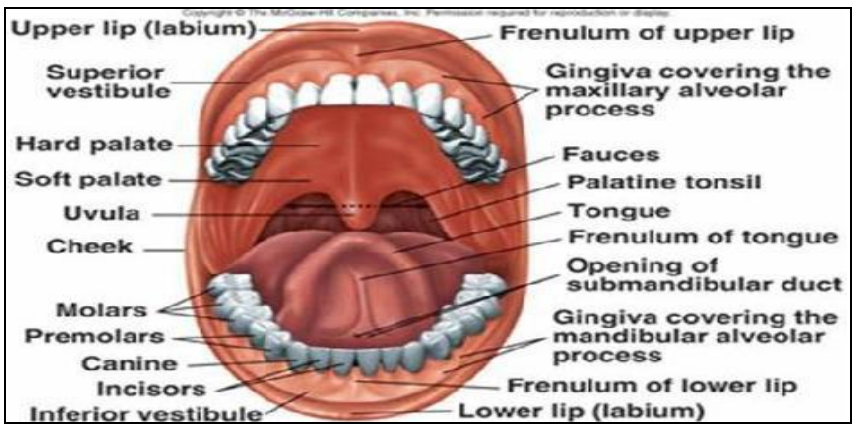

Figure 1: Structure of oral cavity.

Machanism[25]

Mechanisms by which penetration enhancers are thought to improve mucosal absor- -ption are as follows.

Changing mucus theology: 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. 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.

Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption. By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly. Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface.

Advantages of Buccal drug delivery[26]

- It avoids hepatic first-pass metabolism.
- Ease of administration of dosage form.
- It can be It administered to unconscious patient
- Fast onset of action.
- Patient compliance is more.
- Drugs which are not stable in the acidic environment and destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
- It deals with a passive system of drug absorption and does not require any activation.

Limitations of Buccal Drug Delivery System[28]

- Small dose of drug is required.
- Drug that show passive diffusion can only administered by this route.
- Permeability of buccal mucosa is low as compared to sublingual route. Small dose of drug is required.
- Drug have a bitter or unpleasant taste or obnoxious odor or that irritate the mucosa cannot be administered.
- Eating and drinking may mostly restrict.
- Drug which is unstable at buccal environment cannot be given by this roeut
- Permeability of baccalmocosa is low as compared to sublingual route

Mucoadhesion

Mucoadhesion or bioadhesion is defined as the attachment of synthetic or biological macromoleculesto biological tissue. When it is applied to mucosal epithelium bioadhesive interaction When it is applied to mu mucosal epithelium bioadhesive interactin Bioadhesive interaction occur sprimarilywith mucus layer and this is called as mucoadhesion.

Mechanism of Mucoadhesion[28]

Mucoadhesion is two-step process describes theinteraction of mucoadhesive material and mucus membrane. Step 1: contact stage: an intimate contact occursbetweenmucoadhesive and mucus membrane Step 2: consolidation stage: various physic chemical interactions occur to consolidate and strengthen the adhesive joint leading to prolonged adhesion.

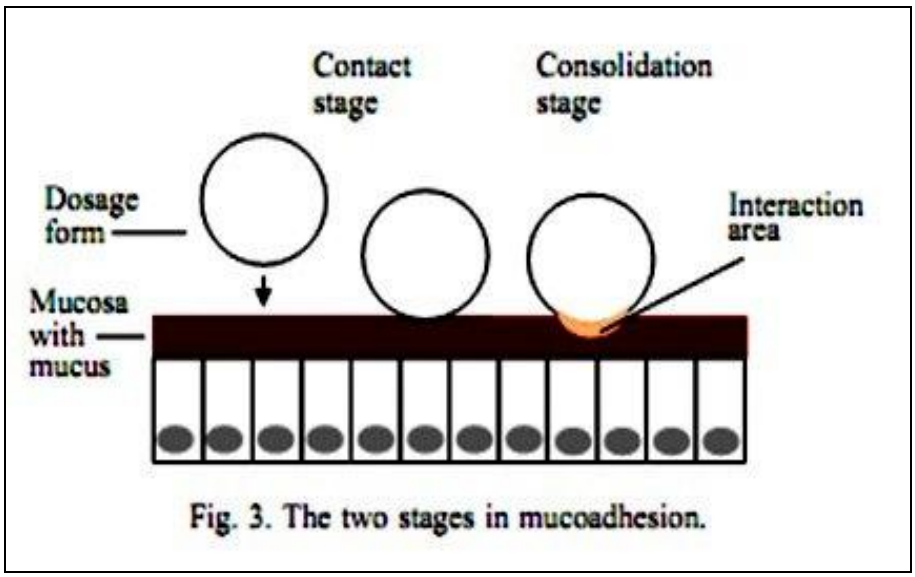

Fig 2: Mechanism of mucoadhesion.

Theories of mucoadhesion

1. Adsorption Theory

According to the adsorption theory, later an initial contact between two surfaces the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be notable. (i) Primary chemical bonds of covalent nature, which are undesirable in mucoadhesion because their high strength may result in permanent bonds. (ii) Secondary chemical bonds contain many different forces of attraction including vander Waals forces, electrostatic forces, hydrogen and hydrophobic bonds.[29]

2. Diffusion theory

As per diffusion theory inter diffusion of polymers chains across an adhesive interface causes adhesion and is driven by concentration gradient. The polymer chains and the mucus coming in contact to a sufficient depth to create a semi-permanent adhesive bond (figure 3). The penetration depends on diffusion coefficient. The diffusion relay on molar weight and decreases rapidly as the cross-linking density increases. For good mucoadhesion some factors are consider those are the chain flexibility, molecular weight, expanded nature of both the mucoadhesive and substrates as well as similarity in chemical structure.[29]

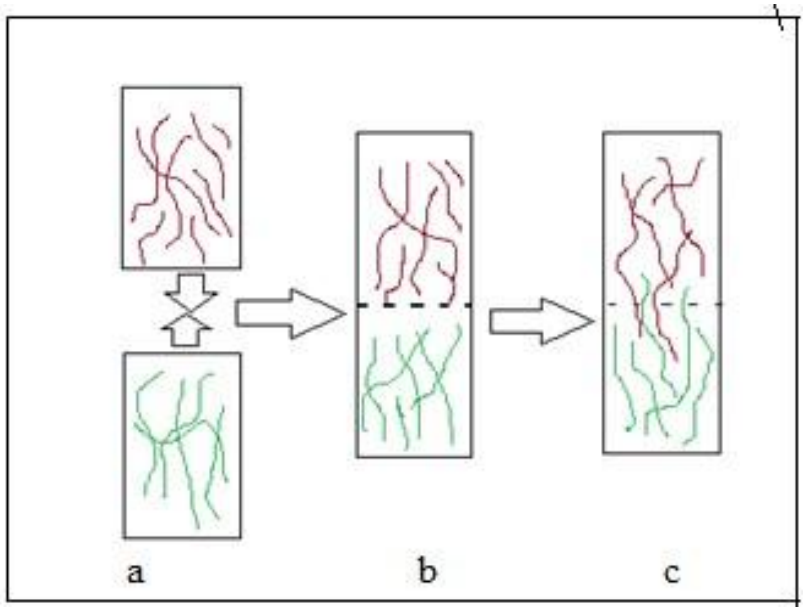

Fig 3: Diffusion theory.

3. Fracture theory

This is most accepted theory in case of mucoadhesion. This theory analyses the force required to detach two surfaces after adhesion. It measures the maximum tensile strength during detachment and it can be expressed by formula given below.[29]

$$G = (E\varepsilon/L)^{1/2}$$

Where E— Young's modulus of elasticity

ε — Fracture energy

L— Critical crack length when two surfaces are separated

G— Fracture strength equation details.

Introduction for Benzocaine

Benzocaine, a para-aminobenzoic acid ester, is a local anesthetic used for surface anesthesia. it has low potency and systemtoxicity. it is used, often in combination with other drugs such as analgesics, antiseptics, antibacterials, antifungals and antipruitics for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, hemorrhoids, anal pruritus and ear pain.[30] it is the active ingredient in many over-the-counter analgesic ointments carbopols, which are very high molecular weight polymers of acrylic acid, have been used mainly in liquid or semi-solid pharmaceutical formulations, such as gels, suspensions and emulsions, as a thickening agent, in order to modify the flow characteristics. Recently, they are also used for their mucoadhesive properties[30] and a relevant amount of work has been done on the bioadhesive potential of carbopol polymers.[30] carbopol 934p is a mucoadhesive polymer which has been investigated as a useful adjuvant for bioadhesivedrug delivery system.[30] The main reasons for addition of mucoadhesive polymers in the system are the possibilities of prolongation of residence time in organ and increase of the contact time with absorbing mucosa, resulting in the enhancement of drug absorption. carbopol 934p is a mucoadhesive polymer and has been investigated extensively by the pharmaceutical industry because of its high viscosity at low concentration as well as its low toxicity.[30] carbopol 934p is a polyacrylic acid polymer, cross linked with allyl sucrose. this acidic carboxylic group partially dissociates in aqueous solution, producing a flexible coil structure. it is a fact that the carbopol gels are prepared by dispersing polymer in water, in which it swells up to 1000 times of the original volume[31] while neutralizing the system. it permits the ionization of carboxylic groups, and as a consequence, a strong gel is formed. The gel formation of carbopol 934p depends on the electrostatic repulsion

between the anionic carboxyl groups.[31] The carbopol 934p gel has the following behavior in aqueous solution:
1) The gel consists of closely packed swollen particles.
2) The gel forms a thick layer that inhibits water penetration.

when a water-insoluble drug has to be added to this gel, it can only be dispersed, and a transparent aqueous phase can beobtained when the insoluble drugs are solubilized in hydrophilic water-miscible cosolvents, e.g., PEG400 and glycerin[32] The drug dissolved in the liquid phase of the gel under a non-ionized form may potentially penetrate more into a barrier like skin or a certain mucosa.[3] If the adhesion is on a mucosal surface, then the phenomenon is called mucoadhesion. This occurs by a process of wetting and interpenetration of the mucoadhesive polymer with the mucus gel.[33, 34] The recent development of mucoadhesive drug formulation permits the drug localization in a particular region, thereby increasing bioavailability and, at the same time, increasing the contact time between drug and mucosa. The purpose of the present investigation was to (a) prepare benzocaine gels using carbopol 934P, (b) study the mucoadhesion power of the formulations having better rheological properties, and (c) compare the release rate and flux of benzocaine between the gel formulations and the commercial sample (Vision-gel)®.

DRUG PROFILE

1) Benzocain[35]

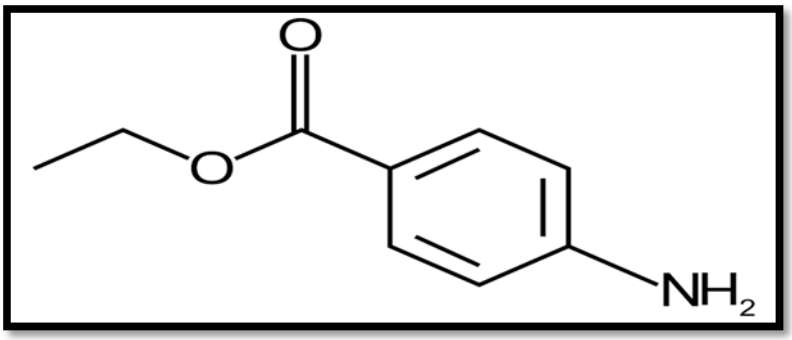

Figure 4: structure of Benzocaine.[35]

IUPAC Name: Ethyl 4-aminobenzoate
Molecular formula: $C_9H_{11}NO_2$
Molecular weight: 165.189g/mol g mol $^{-1}$
pKa: 2.51
Solubility: Very slightly soluble in water, freely soluble in chloroform In ethanol (90%) and in ether.
Appearance: colourless crystals or a white, crystalline powder.
Identification: 1)The infrared absorption spectrum.
2) Melting point
Therapeutic category: local anaesthetics, pain relief, oral ulcer colcor, canker.

Pharmacokinetic Data:- (Pharmacalogy):- Benzocain is a local anaesthetic commonly used as atopicalpain reliever. It is the active ingredient in many over the counter analgesic ointments. It is also indicated for general us as a lubricant and catheters and topical anaesthetic on intratracheal catheters and pharyngeal and nasal airways to obtund the pharyngeal and trachea reflexes; on nasogastric and endoscopic tubes; urinary catheters; laryngoscopes; protoscopes,sigmoid scopes and vaginal specula.[35]

Mechanism of action: Benzocain bind to sodium channel and reversible stabilizes the neuronal membrane which decreases its permeability to sodium ion. Depolarization of the neuronal membrane is inhibited thereby blocking the initiation and conduction of nerve impulse.[35]

Side effect: Adverse effect of Benzocain is generally seizures coma, ireregularheart beat, respiratory depression, pulmonary aspiration, methemoglobinemia anaphylaxis.

2) Carbopol 934[36]

Molecular structure

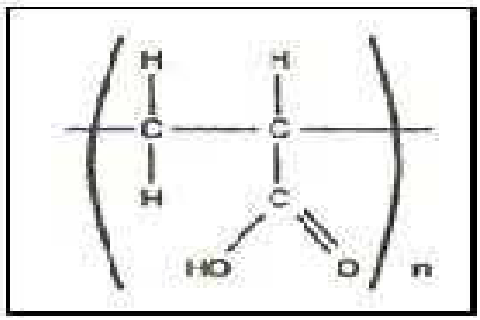

Figure 5: structure of carbopol 934.

Carbopolpolymersare polymers of acrylic acid cross-linked with poly alkenyl ethersordivinyl glycol. They are produced from primary polymer particles of about 0.2 to6.0 micron average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking

Appearance: White, fluffy powder
Odor Slightly acetic Test
Bulk DenSpecific gravity: 1.41
Moisture content: 0% maximumsity
Approximately 208 kg/m3
PKa: 6.0 ± 0.5
Equivalent weight 76 ± 4
Carpool 34 P is cross-linked with alkyl sucrose and is polymerization in solvent benzene.

Rheological properties
1. Cabopol 934 Applications of Carbopol polymers: 130 The readily water-swellableCarbopol polymers are Used in diverse range of pharmaceutical applications to provide:Controlled release in tablets.
2.Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal rectal applications Thickening at very low concentrations to produandce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
3. Permanent suspensions of insoluble ingredients in oral suspensions and topicals. Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.
4. Several properties of Carpool make it potentially valuable as a pharmaceutical
Excipient in numerous applications such as:

Topical Applications
Carbomers are very well suited to aqueous formulations of the topical dosage forms many forms. Many commercial topical products available today have been formulated with these polymers, as they provide the following numerous benefits to topical formulations:
Safe & Effective — Carbopol polymers have a long history of safe and effective use in topical gels, creams, lotions, and ointments. They are also supported by extensive toxicology studies.
Non-Sensitizing — Carbopol polymers have been shown to have extremely low irritancy properties and are non-sensitizing with repeat usage.
No Effect on the Biological Activity of the Drug — Carbopol polymers provide anexcellent vehicle for drug delivery. Due to their extremely high molecular weight,they cannot penetrate the skin or affect the activity of the drug
Excellent Thickening, Suspending, & Emulsification Properties for Topical Formulations.

1) Hydroxy propyl methyl celluse(HPMC K4M)[41]

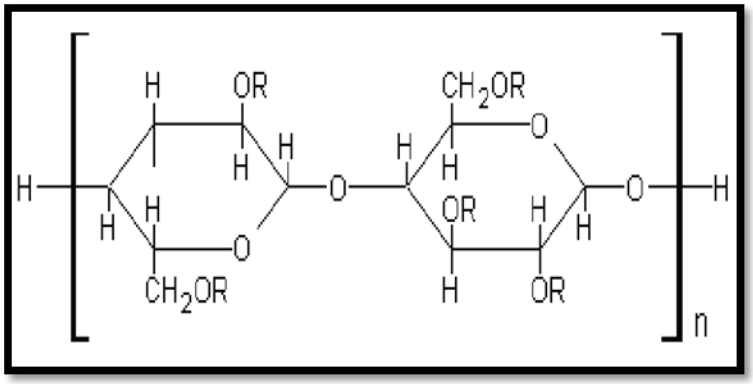

Figure 6: structure of Hydroxyl propyl methyl cellulose.

Non proprietary Name
B.P: Hypromella
U.S.P: Hydroxypropylcelluse
phEur: Methyl hydroxyl cellulosium
Synonym: HPMC, methanol, pharmacoat.
Chemical Name: Cellulose, 2- hydroxyl propyl methyl ether
Category:
Coating agent, film former, stabilizing agent, suspending agent, tablet binder, Viscosity increasing agent.
Description: It is odourless and tasteless, White or creamy White coloured fibrous or granular powder.
Solubility: Soluble in cold water, insoluble in chloroform, ethanol and ether but soluble in mixture of ethcanol and dichloromethane and mixture of methanol chloromethane.

Typical properties
Acidity/alkalinity: ph=5.5-8 for a 1% w/w aqueous solution
Density (bulk): 0.341 g/cm^3
Density (tapped): 0.557 g/cm^3
Density (true): 1.326 g/cm^3
Melting point: brown at 190-200^{0}c chars at 225-230^{0}c
Glass transition temperature: 170-180^{0}c

Moisture Content: Hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and temperature and relative humidity of the surrounding air.
Viscosity: The viscosity of polymer ranges 75 to 140% of declared value.

Safety: It generally regard s nontoxic and non irritant material, although excessive consumption may have a laxative effect.
LD_{50}(mouse,IP):5/kg
LD_{50}(rat,IP)5.2g/kg

Handling consideration: Hypromellose dust may be irritant to eyes and eye protection is recommended.
Stability: It is a stable material material although it is hygroscopic. Increases in temperature reduce the viscosity of solutions.
Storage Conditions: The powder should be stored in well-closed container in a cool and dry place.

Application in pharmaceutical Formulation or Technology
1) Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
2) In oral products Hypromellose is used as a stable binder, in film coating, and as a matrix for use in extended release tablet formulation.
3) Depending upon the viscosity grade, concentration of 2-20% w/w may be used for film forming solution to film coat tablet.
4) It is used as a suspending and thickening agent in topical formulation. It may used may be as a thickening agent ti vehicle for eye drops and artificial tear solution at concentration between 0.45-1.0%w/w.
5) It is used as suspending agent, emulsifier and stabilizer in topical gel and ointment.
6) It is also used in manufacture of capsule, as an adhesive in plastic bandages, and a wetting agent for hard contact lenses.
7) It is also widely used in cosmetics and food products.

4) Glycerin[37, 38]
Structural Formula

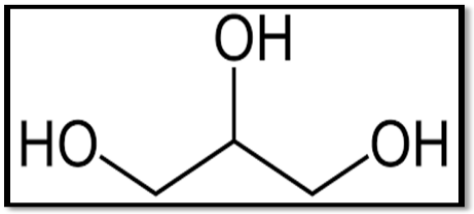

Figure 7: structure of glycerin.

BP: - Glycerol
PhEur : - Glycerol
USP Glycerin
Synonyms:- Croderol; E422; glicerol; glycerine; glycerolum; Glycon G100;Kemstrene Optimpriceerine; 1,2,3- propanetriol: tri-ihydroxypropaneglycerol.
Chemical: - Propane-1, 2, 3-triol
Molecular Formula: - $C_3H_8O_3$
Molecular Weight:- 92.09 g/mol
Functional Category:- Antimicrobial preservative; co-solvent, emollient humectants plasticizer; solvent; sweetening agent; tonicity; agents BPGlycrol
Description:- Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid; ithas a sweettaste, approximately 0.6 times as sweet as sucrose

Typical Properties
Boiling point 2900C (with decomposition)
Density 1.2656 g/cm3 at 150C;
1.2636 g/cm3 at 200C;
1.2620 g/cm3 at 250C
HygroscopicityHygroscopic

Melting point 17.80C
Solubility: - Soluble in water, methanol and Ethanol; slightly soluble in acetone And practically insoluble in benzene Chloroform and oil.

Stability and Storage Condition
Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions, but it decomsesn 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 cool, dry place.

Incompatibilities:- Glycerin may explode if mixed with strong oxidizing agents. Black discoloration of glycerin occurs in the presence of light,or contact with zinc basic bismuth nitrate. An iron cantaminantiglycerin is responsible for the darkening colour of mixture containing phenol, salicylates, andtannin. Safety Generally regarded as a nontoxic and non irritantmaterial.Adverse effects are mainly due to the dehydrating propertie of glycerin. Oral doses are demulcent and mildly laxative in action. Large dosesmayproduce headache, thirst nausea and hyperglycemia. The arenteeraadministration of erylargeglycerindoses, may iinduce hemolysis and renal failure. Sloweraminitration has nodeleterouse effect.

Applications:- In topical pharmaceutical formulations and cosmetic glycerin is used primarily for its humectant and emollient properties used as solvent or co -solvent in creams, emulsions and paranteral Formulations .Also used in gels and adddive in patche applications. In oral solutions, used as a solvent, sweetening agent, antimicribial preservative and viscosity-increasing agent. It is also used as a plasticizer, in film coatings and in production of soft gelatin capsules and gelatin suppositories.

5) Ethanol[39,40]
Structural Formula C_2H_6OH

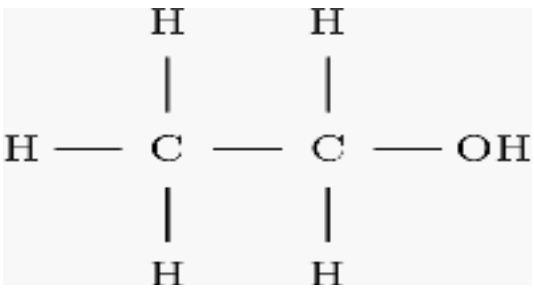

Figure 8: structure of ethanol.

Synonyms alcohol; ethyl hydroxide; grain alcohol; methylcarbinol.
Molecular Formula C_2H_6O
Molecular weight 46.07 g/mol
Functional Category Antimicrobial preservative; disinfectant;skin penetrant; solvent.
Description Alcohol is clear, colorless, volatile liquid with a slight,charactri--stic odor and burningtaste.
Typical Properties
Boiling point 780C
Density 0.789 g/cm3
Melting point -1140C

Solubility:- Miscible with chloroform, ether, glycerin And water (with rise of temperature Contraction of temperature and concenction (vomume) Stability and Storage Conditions Aqueous ethanol solution may be sterilized by autoclaving or filtration and should be stored in airtight containers, in a cool place. Incompatibilities in acidic conditions, ethanol solutions may react vigorously with oxidzing materials. Mixtures with alkali may darken in color due to a Reaction with residual amounts of aldehyde. Ethanol solutions are also incompatible with aluminum containers and may interaction of the some drugs. Safety Ethanol is rapidly absorbed from the GIT a and the vapor may be absorbed through the lungs; it is motabolized mainly in the liver, to acetaldehyde, which is further oxidized to acetate.
Applications:-Ethanol is primarily used as a solvent; it is also employed in solution as an antimicrobial preservative. Topical ethanol solutions are also used aspenetration enhancers and as disinfectants.
It is a stable material material although it is hygroscopic. Increase in temperature reduce the viscosity of solutions.
Storage Conditions
The powder should be stored in well-closed container in a cool and dry place.

Application in pharmaceutical Formulation or Technology
1.Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
In oral products Hypromellose is used as a stable binder, in film coating, and as a matrix for use in extended release tablet formulation.

Depending upon the viscosity grade, concentration of 2-20% w/w may be used for film forming solution to film coat tablet.

It is used as a suspending and thickening agent in topical formulation. It may used may be as a thickening agent ti vehicle for eye drops and artificial tear solution at concentration between 0.45-1.0%w/w.

It is used as suspending agent, emulsifier and stabilizer in topical gel and ointment.

It is also used in manufacture of capsule, as an adhesive in plastic bandages, and a wetting agent for hard contact lenses.

It is also widely used in cosmetics and food products.

AIM AND OBJECTIVES
The aim of this experiment was to formulation and evaluation of mucoadhesive benzocaine gel.

The objectives were
1.To prepare carbopol 934p and HPMC K4M gel.
2.To added benzocaine drug in prepared base.
3.Preparation of benzocaine gel.

MATERIAL AND METHOD
Collection of sample

Sr.No.	Name of drug	Collection
1	Benzocaine	LOBA CHEMIE Mumbai 40005 India PVT.LTD.
2	Carbopol 934	Ozone international Mumbai
3	HPMC K4M	Ozone international Mumbai
4	Glycerine	Ozone international Mumbai
5	Ethanol	Local perches
6	Camphor	Ozone international Mumbai

METHOD OF GEL PREPARATION
Carbopol934 and HPMC K4M were dispersed in ethanol and stirred magnetically .The dispersion was homogenised with bids mechanical stirrer for 15 min.at 300-350 rpm. Then added drug in cabopol and HPMC mixture and stirred for 5min and 1ml of glycerine was added in carbopol mixture and stirred for 10minand then added camphor and phenol and stirred 5min. The resulting gel was neutralise to pH 6.5 by addition of triethanolamine and stirred at 450 rpm until a homogeneous and transparent dispersion gel was formed, and it was stored at 27 and 31°c.

Table 2. composition of benzocaine gel prepared in this study.

Constituent's	% composition (W/W)			
	F1	F2	F3	F4
Benzocaine	0.5	0.5	0.5	0.5
Carbopol 934	0.2	0.3	0.4	0.5
HPMC K4M	0.1	0.1	0.05	0.1
Glycerine	1	1	1	1
Camphor	0.05	0.05	0.05	0.05
Phenol	0.03	0.03	0.03	0.03
Ethanol	q.s	q.s	q.s	q.s

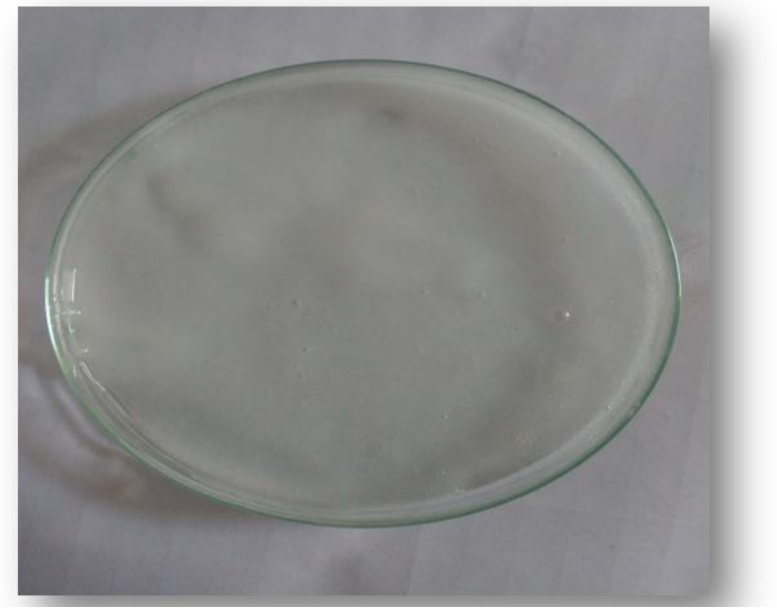

Figure 9: Formulation of carbopol 934+HPMC K4M gel.

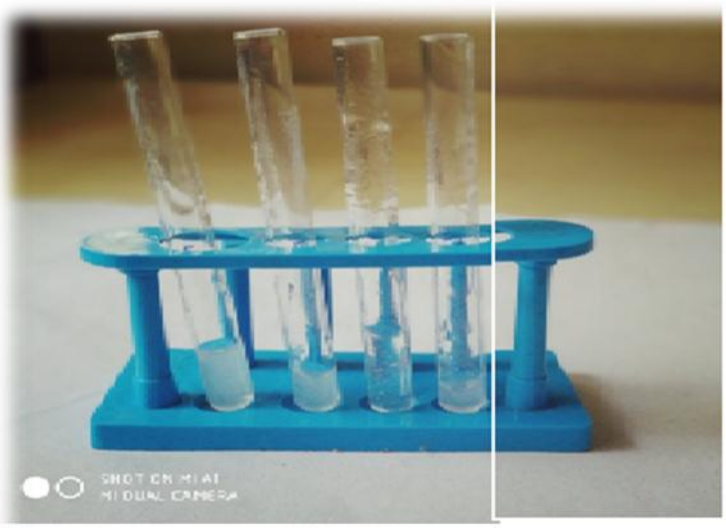

Figure 10: Formulation of Benzocain gel.

EVALUATION STUDIES

4.1. Determination of pH

One g of gel was weighted and diluted 10 times with the hydroalcoholic solution Then the pH was measured.

4.2.Measurement of viscosity of carbopolgel

A Fungi lab viscometer was used to measure the viscosity (pcs) of gel formulations at 27 °C.

4.3. Adhesion strength measurement

The mucoadhesive forces of benzocaine gels were determined by means of the mucoadhesive force-

measuring device shown in Figure 10, and according to the previously reported method[42], using tissue specimen obtained from the mucosal side of the abdominal area of the rat (hairless). The pieces of tissues were stored frozen in phosphate buffer at pH 7.4, and thawed to the room temperature before use.[43] At the time of testing, a section of rat skin (E) was secured (keeping the mucosal side out) to the upper of a glass vial (C) using a cyanoacrylate adhesive. The diameter of each exposed mucosal membrane was 1.5 cm.

The vials were equilibrated and maintained at 37 °C for 10 min. After that, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). To the exposed surface of the tissue attached on the vial, a constant amount of 0.1 g benzocaine gel (D) was applied. Before applying the gel, 150 µl of stimulated saliva solution (2.38 g $NaHPO_4$, 0.19 g KH_2PO_4 and 8 g NaCl in 1000 ml of distilled water adjusted to pH=6.75) was evenly spread on the surface of the test membrane. The height of the vial was adjusted so that of the gel could adhere to the mucosal surface of the both vials. Immediately, a constant force of 0.5 N was applied for 2 min. to ensure intimate contact between the tissues and the samples. The upper vial was then moved upwards at a constant speed, while it was connected to the balance. Weights were added at a constant rate.

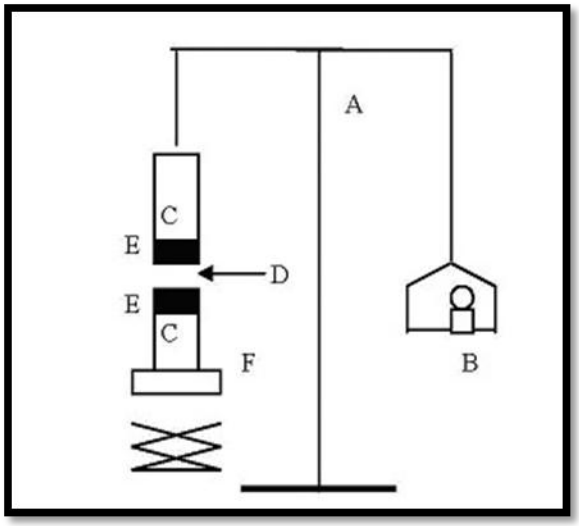

Figure 11. Bioadhesive force-measuring device: (A) modified balance; (B) weights; (C) glass vial; (D) benzocaine gel; (E) rat tissue; (F) height-adjustable pan.

to the pan on the other side of the modified balance until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm^2, was determined from the minimal weights needed to detach the tissues from the surface of each formulation, using the following equation.[42]

$$\text{Detachment Stress (dyne/cm}^2) = \frac{m.g}{A}$$

Where *m* is the weight added to the balance in grams; *g* is the acceleration due to gravity taken as 980 *cm/s*^{2}; and *A* is the area of tissue exposed. Measurments were repeated three times for each of the gel preparations, while before each measurement a fresh smooth gel surface was created. Effect of varying contact time (1, 2, 3, 5 and 10 min.) was investigated for some of the gel preparations to optimize initial contact time. In brief, formulations were allowed to be in contact with mucosa for carrying contact times (1, 2, 3, 5, and 10 min.), and the bioadhesive force was determined as discussed above. Contact time that resulted in maximum bioadhesive strength was selected as optimum contact time required for adequate adhesion. All of the abovementioned experiments were conducted in triplicates.

4.4 Assay procedures

4.4.1. Analytical method for the assay of benzocaine

In order to determine the standard calibration curve of benzocaine, a stock of 1 mg/ml was prepared. Then, dilutions were made to prepare a series of solutions containing benzocaine in different concentrations. In these solutions, absorbance values at 291 nm (l_{max}) were determined spectrophotometrically. The calibration curve of benzocaine was prepared by plotting the concentration values (*x)* versus absorbance values *(y*). Analytical parameters for the assay of benzocaine were calculated using ANOVA test.

4.4.2. Recovery studies

The study the accuracy, reproducibility, precision and to check the interference with the excipients used in the formulation, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the gels and the mixtures were analyzed spectrophotometrically. Percentage of recovery was calculated after three experiment.

RESULT AND DISCUSSION

5.1. The effect of pH:- Aqueous dispersions of carbopol (0-3%) exhibited pH values between 2.8 to 6.5, at 27 °C. In general, increasing the carbopol concentration (higher carboxyl concentration) caused increase of the gel viscosity, because of the ionization of carboxylic groups, and as a consequence a strong gel then formed. The pH of all of the formulations was adjusted to 6.5 with triethanolamine. The pH of the gel was measured and adjusted to pH between 3-7, because benzocaine is hydrolyzed in strong acidic and alkaline conditions and may also damage the mucosa.

Table 3.pH of benzocaine gel.

Sr no.	Formulation codes	pH
1.	F1	5.1
2.	F2	5.4
3.	F3	6.7
4.	F4	6.5

5.2. The effect of viscosity

The viscosity of 0.5% carbopol gels of various pH was determined at various shear rates. As the shear rate increased the viscosity of carbopol gel decreased. Results show the viscosity of carbopol gel of various concentrations and various pH.

3). Also, the increase in carbopol concentration to about (0.4%) caused increase of viscosity and higher concentrations showed slight increase of viscosity. Findings indicated that marked differences were noted in viscosity of carbopol gels of various pH. The increase of pH in various concentrations of carbopol gels show.increased viscosity, showing the highest viscosity when neutralized to pH 6. This finding is related to the increase in ionization as a result of increase in electrostatic repulsion between adjacent carboxylic groups and the subsequent expander polymer network.[44,45] Nonneutralizedcarbopol gels showed significantly weaker gel structure, as expected, due to the constricted gel network.[44] The structures of these non-neutralized systems are predominantly built up by hydrogen bonds, which are easily breakable under shear stress.

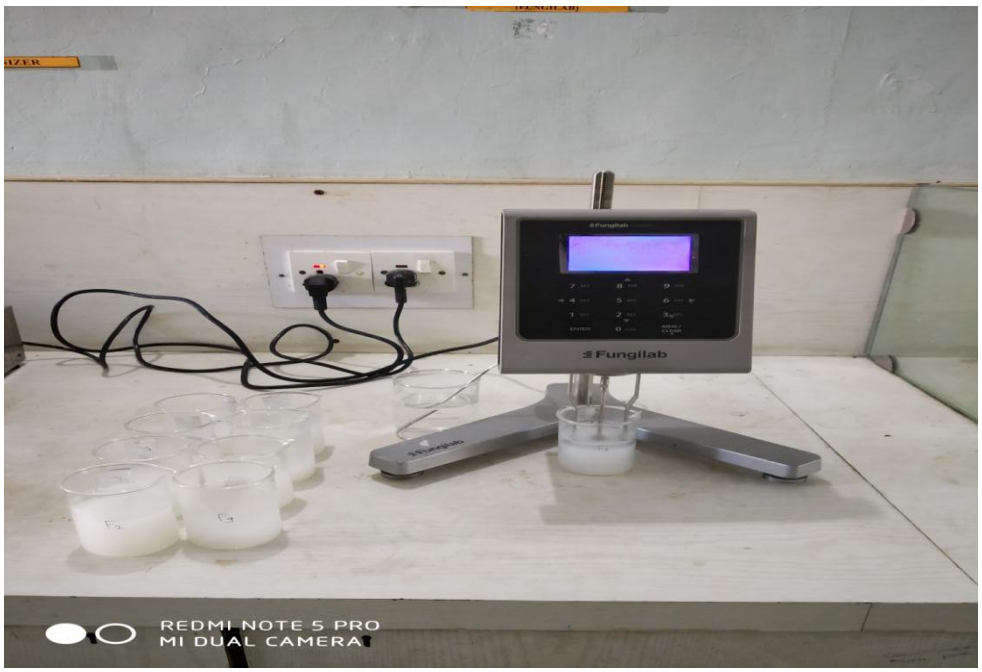

Figure 12: Viscometer.

Table 4.Viscosity of benzocain gel.

Formulation codes	Viscosity(CPS)
F1	4700 CPS
F2	3500 CPS
F3	5600 CPS
F4	6900 CPS

5.3 FTIR Spetroscopy

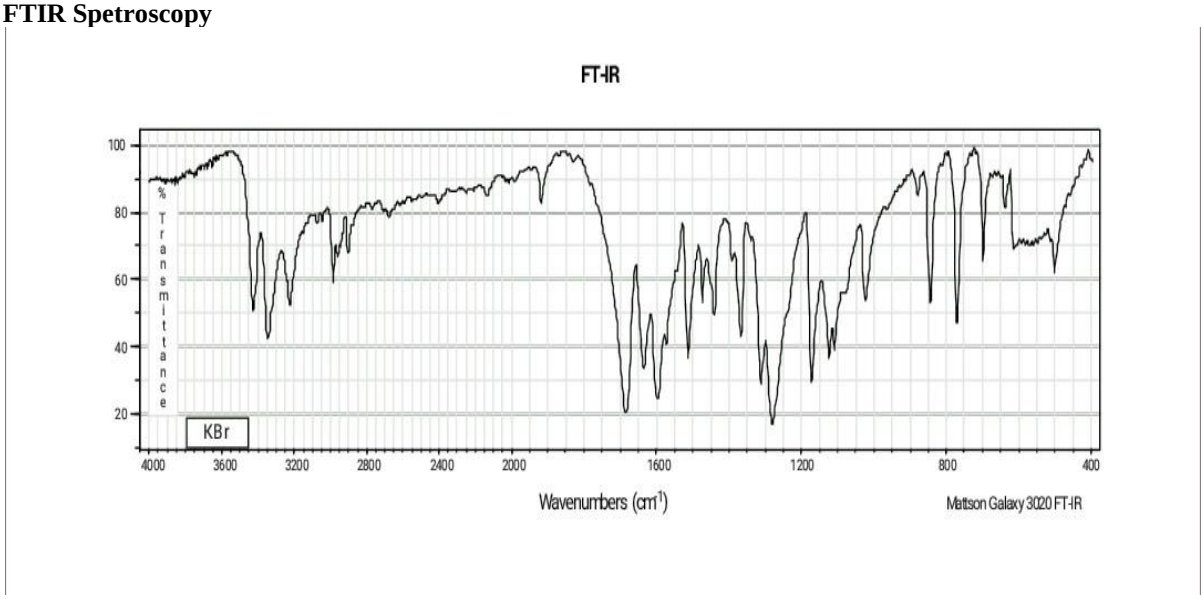

Figure 13: FTIR Spectra of Benzocain.

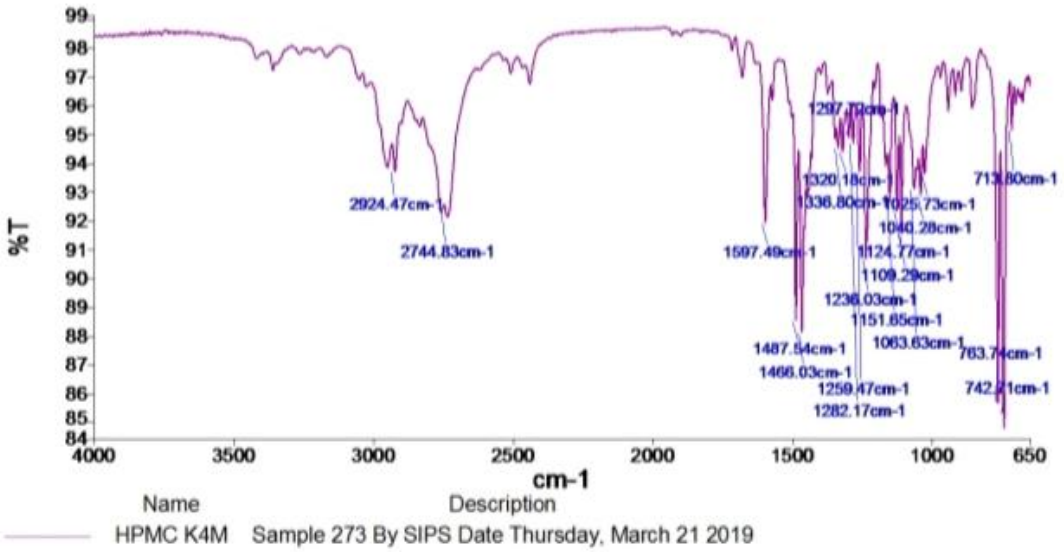

Figure 14: FTIR of HPMC K4M.

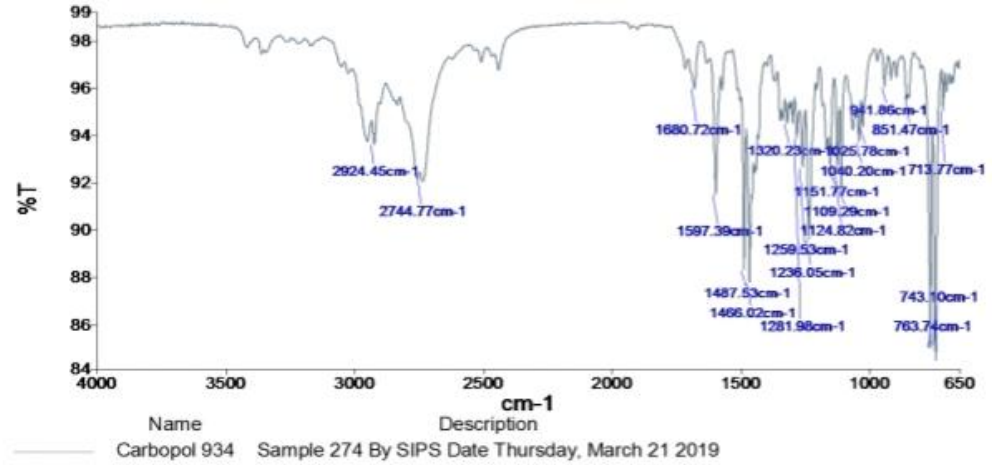

Figure 15: FTIR of carbopol 934.

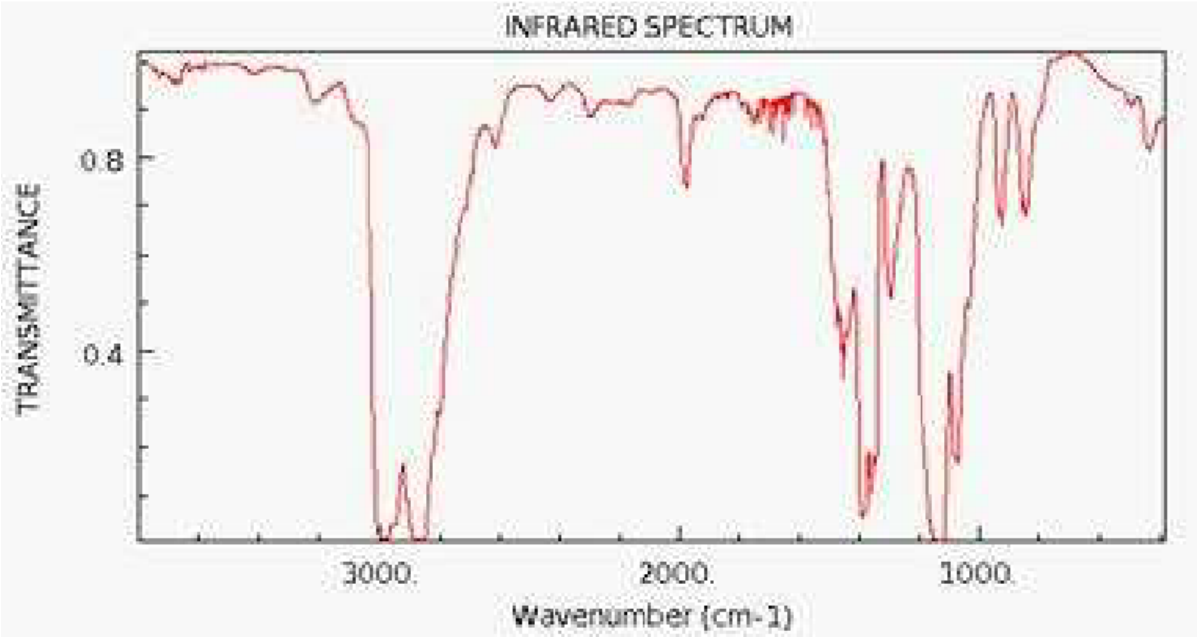

Figure 16: Benzocain and HPMC K4M.

5.3. Mucoadhesion force

The mucoadhesive force is an important physicochemical parameter for local anesthetic used for surface anesthesia.[46] The effect of different concentrations of benzocaine gel formulation on mucoadhesive force is shown in Table 5. The bioadhesive force has significantly increased as the concentration of mucoadhesive polymers increased over the range of 0.2-0.5 % (p<0.05). The maximum mucoadhesive strength could be showed at0. 2-0.5% concentration of carbopol and similar results are reported.[47] Furthermore, Ahuja*et al.*[48] stated that high molecular weight is important to maximize adhesion through entanglementsand Van der Waals forces. The reinforcement of the mucoadhesive forces of gel by the used polymer could be explained by the fact that secondary bond forming groups (e.g. hydroxyl, ether oxygen and amine) are the principle source of mucoadhesion.[49,50]

Table 5. Effect of different concentrations of carbopol 934p in formulation on themucoadhesive force of benzocaine gel.

Concentration (%)W/W	Mean mucoadhesive force (dyne/cm^2) 10^3 SD
0.2	1.852 0.428
0.3	4.102 0.596
0.4	4.872 0.916
0.5	6.347 0.587

5.4. Results of assay procedures

5.4.1. Assay of benzocaine

Calibration curve is Analytical parameters for the determination of benzocaine by UV spectrophotometric method,at the wavelength 291.4 nm.

Table 6. Calibration curve of benzocaine.

Sr.No	Concentration	Absorbance
1	0.5	0.125
2	1.0	0.228
3	1.5	0.340
4	2.0	0.340
5	2.5	0.54
6	3.0	0.631

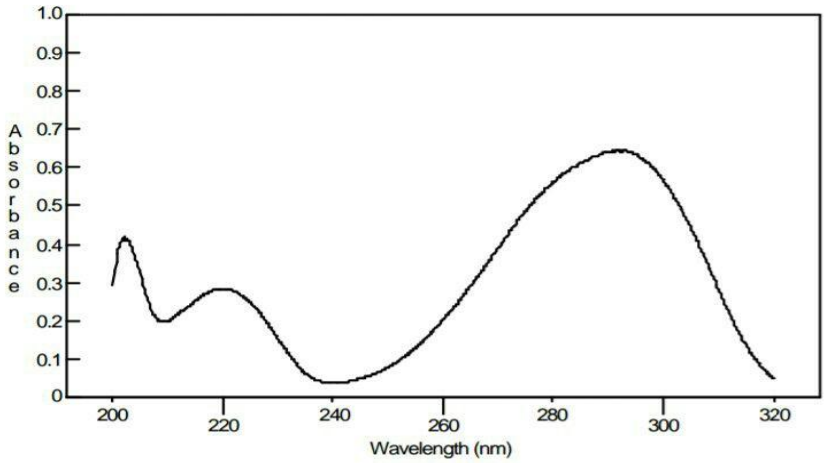

Figure 1: UV Spectra of Benzocaine.

5.4.2 Diffusion studies

The diffusion studies is done by franz diffusion cell, As follows;

Table 7. Diffusion Studies.

Sr.No	Batches	Percentage of drug diffusion
1	F1	89%
2	F2	90%
3	F 3	93%
4	F4	81%

CONCLUSION

Carbopol 934p and HPMC K4M are the most common thickening agents for alcohol phases. It is used after neutralization and its mucoadhesive properties in the aqueous medium are well known. Carbopol 934P system with different concentrations showed different release characteristics. In fact, generally, carbopol-water system has higher release rate. Benzocaine penetrates through the mucosal surface of buccals and in this environment exerts its mucosal pain release, mouthulcer, anesthesia, and antibacterial etc. Gel formulation of benzocaine with mucoadhesive properties is promising for prolonging buccal residence time and thereby higher oral absorption. In addition, they provide intimate contact between a dosage form and the absorbing tissue which may result in high drug concentration in local area and hence high drug flux through the absorbing tissue.

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