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Review Article

Therapeutic effectiveness and development of eugenol topical gel to reduce irritant effect on skin

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ABSTRACT

The present study was designed to formulate and evaluate different formulae of topical gel containing eugenol for treatment of skin disorder as acne. The gel was formulation was optimized by using different polymers with different concentration of hydroxyl propyl methyl cellulose (HPMC), carbopol, and xanthan gum. In these all polymer, carbopol polymers were suitable for formulation in different concentration such as 1%, 2% and 3%. Five different formulae were prepared and characterized physically in terms of colour, pH, homogeneity, drug content, in-vitro drug release. Drug was identified by the IR and Mass. These are also identified by UV.

Keywords: Eugenol, carbopol, Infrared spectroscopy (IR), Ultraviolet spectroscopy study (UV)

INTRODUCTION

Topical preparations are used for the localized effects at the site of their application by quality of drug penetration into the underlying layers of skin or mucous membranes. The major advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous indication of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical drug delivery systems include a large diversity of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments.[1, 2]

Topical delivery is an attractive route for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. It can penetrate deeper into skin and hence give better absorption.

Topical application has many benefits over the conventional dosage forms. Topical preparations avoid the GI-irritation, prevent the metabolism of

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drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. Gel formulation provides better application property and stability in comparison to cream and ointment. Skin is one of the most large and readily accessible organs on human body for topical administration and is main route of topical drug delivery system.

A topical medication is a type of medication that is applied to a particular place on body surface or in the body. Most often topical administration means application to body surfaces such as the skin or mucous membranes to treat disease via a large range of classes including creams, foams, gels, lotions, and ointments. Many topical medications are epicutaneous, meaning that they are applied directly to the skin. Topical medications may also be inhalational, such as asthma medications, or applied to the surface of tissues other than the skin, such as eye drops applied to to the surface of tissues other than the skin, such as eye drops applied to the conjunctiva, or ear drops placed in the ear, or medications applied to the surface of a tooth. The word *topical* derives from Greek *topikos*, "of a place". The conjunctiva, or ear drops placed in the ear, or medications applied to the surface of a tooth**.** [3]

GEL

Gels are a relatively newer class of dosage form designed by entrapment of large amounts of aqueous or hydroalcholic liquid in a network of colloidal solid particles which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Carbomers that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water. Gel is two-component system of a semisolid nature rich in liquid. Although different authors emphasize various properties within their definitions, the one common feature that they identify as characteristic of a gel is the presence of some form of continuous structure, which provides solid-like properties. In a typical polar gel, a natural or synthetic polymer at a relatively low concentration (usually much less than 10%) builds a three-dimensional matrix throughout a hydrophilic liquid. The system may be clear turbid, because the gelling agent does not fully dissolve or because it forms aggregates which disperse the light. Gels are semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels are a substantially dilute cross-linked system, which exhibits no flow when in the steady- state.

Properties of gels:

- It should be inert, compatible with other additives and non-toxic.
- It should be stable at storage condition.
- It should be free from microbial contamination.
- It should maintain all rheological properties of gel.
- Economical.
- It should be washable with water and free from staining nature.
- It should not affect biological nature of drug.
- It should be convenient in handling and its application.
- It should possess properties such as thixotropic, greaseless, emollient, non-staining etc.[4]

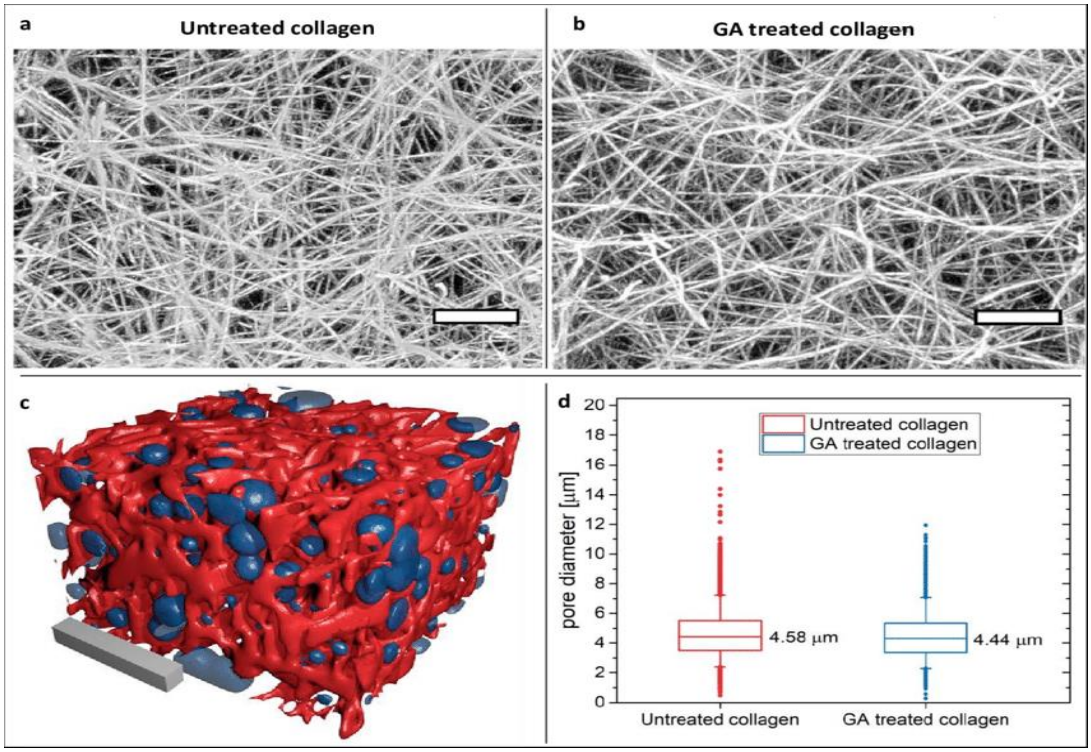
Structure of gels: A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin. The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel.

Topical gel formulations have three main functions:

- To help hydrate skin because of their emollient properties.
- To protect from external environment or heal an intact or injured area of the skin.
- To deliver medication to the skin

Characteristics of gels: Gels should possess the following properties

- Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.
- The gelling agent included in the preparation should produce a reasonable solid- like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- It should possess suitable anti-microbial activity against microbial attack.
- The topical gel should not be tacky.
- The gels intended for ophthalmic use should be sterile.



Source;https://www.researchgate.net/publication/331901933/figure/fig1/AS:738525477605378@1553089603605/Overall-gel-structure-and-pore-size-determination-in-LSM-stacks-of-untreated-a-and-GA.png
Fig 1 Structure of gels

Swelling: When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages.

Syneresis: Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as Syneresis. The degree, to which Syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

Ageing: Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent. In gels, ageing results in gradual formation of a denser network of the gelling agent. Theimer suggests that this process is similar to the original gelling process and continues after the initial gelation, since fluid medium is lost from the newly formed gel.

Structure: The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which determines the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregate of small molecules, or single macromolecules.

Rheology: Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting Non Newtonian flow behavior, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by n gels, ageing results in gradual formation of a denser network of the gelling agent.[5]

About Drug (Eugenol)

Eugenol is an essential oil extracted from the clove plant," Syzygium aromaticum". Eugenol, a phenolic photochemical extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, basil and bay leaf, have a range of antimicrobials to anticancer activity. It is extracted from the leaves and buds of "Eugenia caryophyllata." It is known as eugenol. Now days, eugenol can also be synthesized in laboratory scale

and industrial scale by allylation of guaiacol with allyl chloride having the similar type of functional property.[6]

Source;
https://5.imimg.com/data5/BL/BF/NA/SELLER-7939902/clove-oil-rectified--500x500.jpeg

Fig 2 Structure of Eugenol

Eugenol (4-allyl-1-hydroxy-2-methoxybenzene) is a well-known natural product occurring in many angiospermic plants with a pleasant smell and spicy taste. Eugenol have aromatic flavor. Eugenol belongs to the group of phenylpropanes such as anethol, estragole and cinnamaldehyde, which is biosynthesized by the shikimate pathway.

Eugenol is slightly soluble in water, a essential for all medicinal purpose. It is used as a flavoring agent in the foods, similar all phenols, eugenol is an antiseptic, used as bactericide in mouthwash. Expected to its analgesic and antiseptic properties, it is used in dentistry; it is mixing with zinc oxide it forms cement for temporary fillings of the teeth.[7]

Eugenol is known to have several pharmacological properties i.e, anaesthetic, antioxidant, antimicrobial, antihelmintic, anti-inflammatory, anticarcinogenic, antifumigant, and antirepellent properties. It has been in use as a conventional remedy for tooth ache and also for medicinal and edible purposes. This multiskilled molecule is a key ingredient in perfumes, cosmetics, flavorings agents.[8]

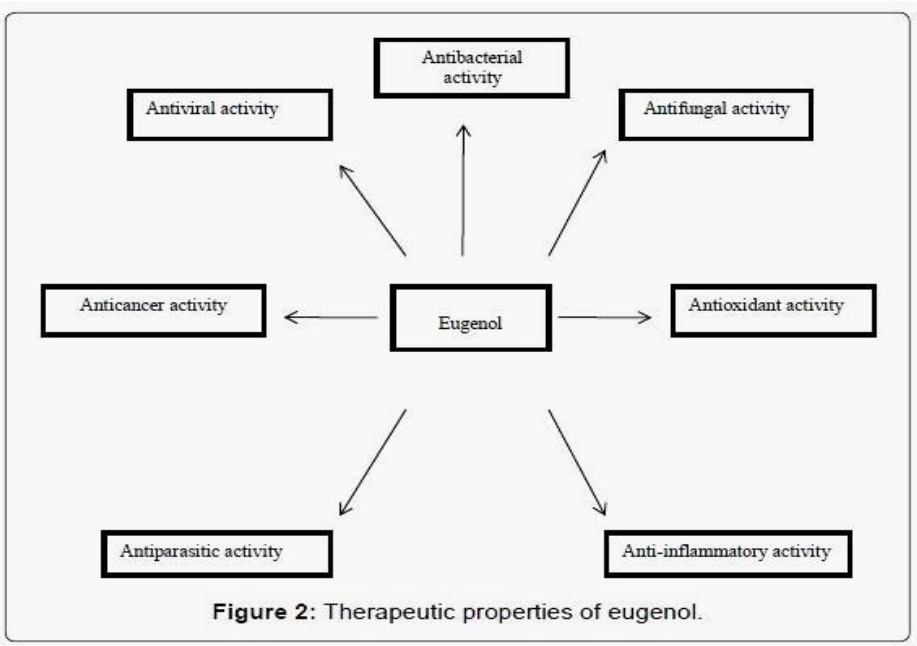


Fig 3 Therapeutic properties of euenol

Eugenol is mainly prepared from natural oil sources by mixing the essential oil with an excess of aqueous sodium (3%) or potassium hydroxide solution and shaking, leading to the formation of a phenolic alkali salt. The insoluble non- phenolic portion is then extracted with a solvent or by steam distillation. The undissolved portion is removed, the alkali solution acidified at low temperatures and the discharged eugenol purified by fractional distillation, thin layer chromatography, high pressure liquid chromatography. The presence and purity can be checked by FTIR, NMR and MASS spectroscopy.

DISEASE (ACNE)

Acne vulgaris is a long term disease of the pilosebaceous follicle denoted by non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). Its pathogenesis is multifactorial - the interplay of hormonal, bacterial, and immunological (inflammatory) factors results in the formation of acne lesions. Acne affects skin having dense sebaceous follicles in areas including face, chest and back. While acne is not a life-threatening condition, it can have harmful effects on the quality of life of affected individuals. Fortunately, acne is

readily responsive to the wide-range of available medications, with the goals of therapy being to clear the lesions, prevent scarring, and limit any treatment-related side-effects and psychosocial sequelae. Newer fixed-dose combination products target multiple acne pathogenic factors and offer simplified dosing system, which may potentially enhance both efficacy and patient adherence when compared with single agent therapy.[9]

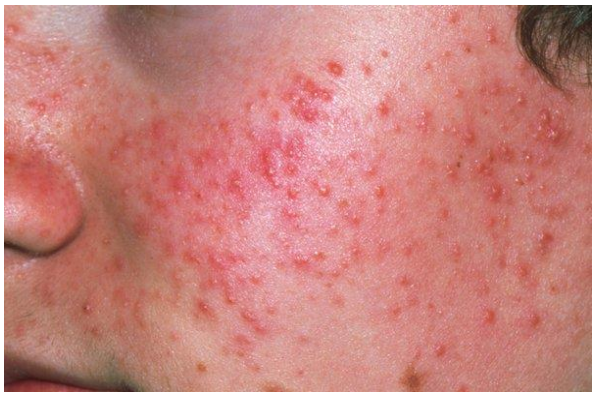


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Fig 4 Structure of Acne

Acne may be classified according to predominance of specific skin lesions:

→ Comedonal (non-inflammatory) – mild
→ Papular (inflammatory) – mild-to-moderate
→ Pustular (inflammatory) – moderate
→ Nodulocystic – severe.[10]

The pathogenesis of acne vulgaris involving more factors such as

→ Follicular epidermal hyperproliferation with subsequent plugging of the follicle.
→ Excess sebum production.
→ The presence and activity of the commensal bacteria Propionibacterium acnes.
→ Inflammation.

Acne develops as a result of bacterial overgrowth and inflammation in the pilosebaceous units. The body's hormone level changes pilosebaceous gland function and causes acne.

Androgens are causative factors for acne which induces sebum production leading to the comedones development. Changes in the skin's natural flora are linked with androgen related sebum production. Diseases like congenital adrenal hyperplasia, polycystic ovarian syndrome and endocrine tumors result in a high level of androgens in body and associated with the development of acne vulgaris.

Propionibacterium acnes is an anaerobic organism present in acne lesions. The presence of Propionibacterium acnes promotes inflammation through a variety of mechanisms.

Propionibacterium acnes stimulate inflammation by producing proinflammatory mediators that diffuses through the follicle wall.

Propionibacterium acnes (P. acnes) are anaerobic bacterium species that mainly causes acne. Staphylococcus aureus has been discovered to play an important role since normal pores colonized only by Propionibacterium acnes. Specific clonal sub strains of Propionibacterium acnes are also associated with normal skin health and long term acne problems.[11-14]

Objective of work

Today, Hydrogels still fascinate material scientists and biomedical researchers have been made in term of their formulations and uses. Hydrogel are unique preparation, they consist of a self-supporting, water-swollen, three-dimensional viscoelastic network which allow the diffusion and attachment of molecules and cells.[15] Hydrogel have recently drawn great attention for use in a wide variety of biomedical application such as cell therapeutics, wound healing, bone regeneration and sustained release of drugs. This is due to their biocompatibility and the similarity of their physical properties to natural tissue.[16]

From commitment of researcher inventive work to the most recent hydrogel- based innovation and products on the market, it imparts the reader with an exhaustive summary of the topic. Widespread application of these products in various industrial and environmental areas is thought to be of major importance.

HYDROGEL

Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. Hydrogels can be made from essentially any water-soluble polymer, surrounding a wide range of chemical compositions and bulk physical properties. Hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films.

Hydrogels are commonly used in clinical practice and experimental medicine for a wide range of applications, including tissue engineering and regenerative medicine, diagnostics, cellular immobilization, separation of biomolecules or cells, and barrier materials to regulate biological adhesions.

The unique physical properties of hydrogels have sparked particular interest in their use in drug delivery applications. Their highly porous structure can easily be tuned by controlling the density of crosslinks in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Biocompatibility of hydrogel promoted by the high water content of hydrogels and the physiochemical similarity of hydrogels to the native extracellular matrix, both compositionally (particularly in the case of carbohydrate-based hydrogels) and mechanically. Biodegradability or dissolution may be designed into hydrogels via enzymatic, hydrolytic, or environmental (e.g. pH, temperature, or electric field) pathways, however, degradation is not always desirable depending on the time scale and location of the drug delivery device. Hydrogels are also relatively deformable and can conform to the shape of the surface to which they are applied. [17-20]

1.5 Classification of hydrogel

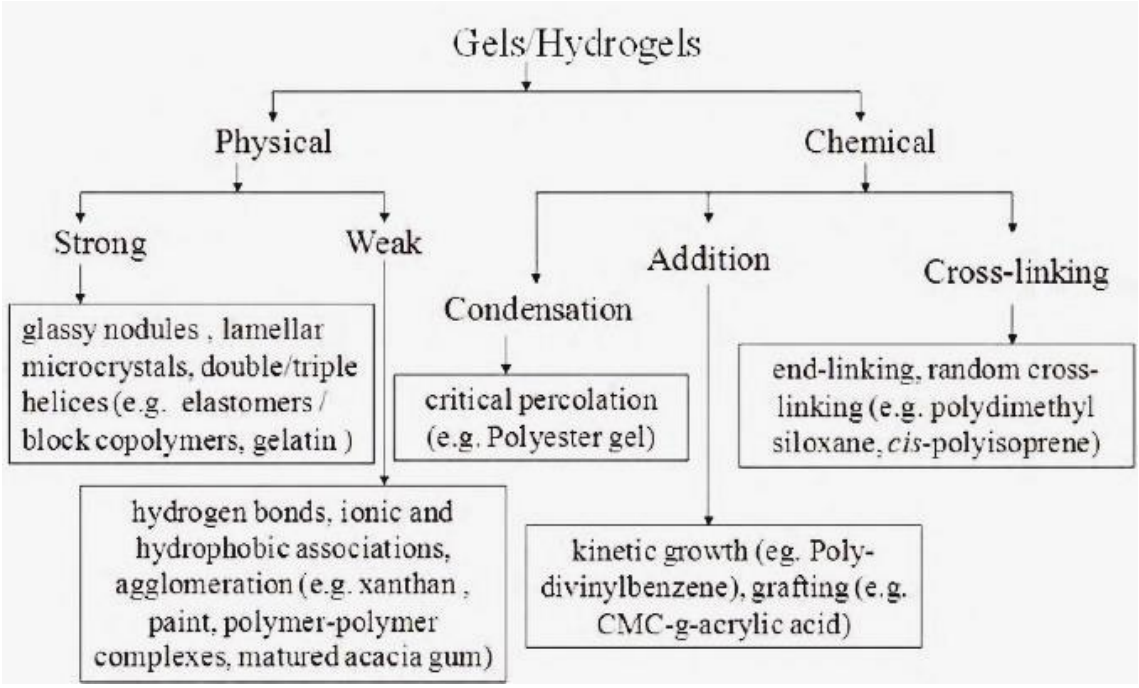

Fig. 5 Classification of hydrogel

Characteristics of hydrogel

- The water holding capacity and permeability are the most important characteristic features of a hydrogel. The polar hydrophilic groups are the first to be hydrated up water which leads to the formation of primary bound water. As a result the network swells and exposes the hydrophobic groups which are also capable of interacting with the water molecules. This leads to the formation of hydrophobically-bound water, also called 'secondary bound water'. Primary and secondary bound water are often combined and called 'total bound water'. The network will absorb additional water, due to the osmotic driving force of the network chains towards infinite dilution.
- This additional swelling is opposed by the covalent or physical cross-links, leading to an elastic network retraction force. Thus, the hydrogel will reach an equilibrium swelling level.
- The additional absorbed water is called 'free water' or 'bulk water', and assumed to fill the space between the network chains, and/or the centre of larger pores, macropores, or voids. Depending on the nature and composition of the hydrogel the next step is the disintegration and/or dissolution if the network chain or cross-links are degradable.
- Biodegradable hydrogels, containing labile bonds, are therefore advantageous in applications such as tissue engineering, wound healing and drug delivery. These bonds can be present either in the polymer backbone or in the cross-links used to prepare the hydrogel.
- The labile bonds can be broken under physiological conditions either enzymatically or chemically, in most of

the cases by hydrolysis. Biocompatibility is the third most important characteristic property required by the hydrogel. Biocompatibility calls for compatibility with the immune system of the hydrogel and its degradation products formed, which also should not be toxic. Ideally they should be metabolized into harmless products or can be excreted by the renal filtration process. Generally, hydrogels possess a good biocompatibility since their hydrophilic surface has a low interfacial free energy when in contact with body fluids, which s in a low tendency for proteins and cells to adhere to these surfaces. Moreover, the soft and rubbery nature of hydrogels minimizes irritation to surrounding tissue. The cross-links between the different polymer chains results in viscoelastic and sometimes pure elastic behavior and give a gel its structure (hardness), elasticity and contribute to stickiness.

- Hydrogels, due to their significant water content possess a degree of flexibility similar to natural tissue. It is possible to change the chemistry of the hydro gel by controlling their polarity, surface properties, and mechanical property contact.

Advantages of hydrogel

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc.
- Achievement of efficacy with lower total daily dosage of drug by continuous drug input.
- Avoids fluctuation in drug levels, inter- and intra-patient variations.
- Ability to easily terminate the medications, when needed.
- A relatively large area of application in comparison with buccal or nasal cavity
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Improved physiological and pharmacological response.
- Improve patient compliance. Provide suitability for self-medication.[21]

METHOD TO PRODUCE HYDROGEL

Heating/Cooling a polymer solution

Physically cross-linked gels are formed when cooling hot solutions of gelatin or carrageenan. The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation.

Upon cooling it transforms rigid helical rods. In presence of salt (K^+, Na^+, etc.), due to screening of repulsion of sulphonic to group (SO^{-3}), double helices further aggregate to form stable gels (Figure 2.2). In some cases, hydrogel can also be obtained by simply warming the polymer solutions that causes the block copolymerization. Some of the examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogen.

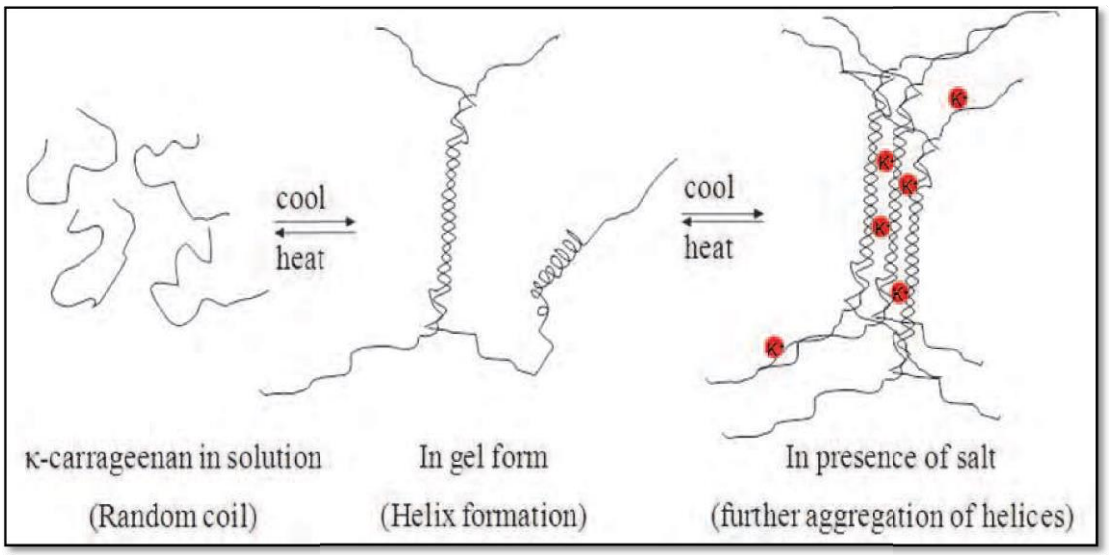

Fig.6 Mechanism of gel formulation in presence of electrolyte

Ionic interaction: Ionic polymers can be cross-linked by the addition of di- or tri-valent counter ions. This method underlies the principle of gelling a electrolyte solution (e.g. Na^+ alginate-) with a multivalent ion of opposite charges (e.g. Ca^{2+} + $2Cl^-$).

Complex coacervation: Complex coacervate gels can be formed by mixing of a polyanion with a polycation. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions.

H-bonding: H-bonded hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. Examples of such hydrogel is a hydrogen-bound CMC (carboxymethyl cellulose) network formed by dispersing CMC into 0.1M HCl. the mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding. The hydrogen bonds induce a decrease of CMC solubility in water and result in the formation of an elastic hydrogel.

Carboxy methylated chitosan (CM-chitosan) hydrogels can also prepared by cross linking in the presence of acids or poly functional monomers. Another example is polyacrylic acid and polyethylene oxide (PEO-PAAC) based hydrogel prepared by lowering the pH to form H-bonded gel in their aqueous solution. In case of xanthan-alginate mixed system molecular interaction of xanthan and alginate causes the change in matrix structure due to intermolecular hydrogen bonding between them resulting in formation of insoluble hydrogel network.[22]

EVALUATION OF HYDROGEL

Appearance: The Gel formulated is observed for their visual appearance, colour, texture feel. upon application such as grittiness, greasiness, stickiness, smoothness, stiffness and tackiness.

Determination of pH: The pH of the gels is determined by immersing pH meter to a depth 0.5 cm in a beaker containing gel. The determinations were carried out in triplicate and the average of three reading is recorded.

Viscosity: The viscosity determinations are carried out by Brook-field viscometer.

Spreadibility: The parallel plate method is the most widely used method for determining and quantifying the spreadibility of semisolid preparations. The advantages of the method are simplicity and relative lack of expense. Also, the assemblies can be designed and fabricated according to individual requirements to type of data required. On other hand, the method is less precise and sensitive, and the data it generates must be manually interpreted and presented. Validated the spreading diameter measurements of hydro gels on the basis of cellulose derivatives and established the linearity of spreading diameter measurements. The linear relationship between viscosity and spreading diameter was independent of the derivative. The spreading capacity of the gel formulations was measured 48 h after preparation by measuring the spreading diameter of 1 g of the gel between two 20×20 cm glass plates after 1 min. the mass of the upper plate was standardized at 125 g. Panigrahi et al. used a similar apparatus to assess the spreadibility of gels.

Drug content: Gel formulations (100 mg) was dissolved in methanol and filtered and the volume was made to 100 ml with methanol. The resultant solution was suitably diluted with methanol and absorbance was measured at 249 nm using Shimadzu –1700 UV Visible spectrophotometer. Drug content was determined from calibration curve for MOF.

Drug content uniformity: To determine the drug content uniformity, the sample is taken from top, middle, and bottom of the container. Are further assay is done to determine uniformity in label claim.

In-vitro drug diffusion study: Franz diffusion cell maintained at 37 ^oC are used for in-vitro drug release study.

Procedure

- Before starting the study the cells are calibrated for their volume capacity.
- These are hydrated in drug release media.
- Membranes are removed out and dried in oven at 30-35^oC.
- The gel preparation to be evaluated is poured in a 2 ml needle. 100-500 mg gel is forced through needle to membrane and weighed on a weighing balance.

Cells are filled with media, and placed one magnetic bead is placed in cell. Cell are allowed to equilibrate at experimental temperature for 30 min. Membrane is placed over the cell. Donor cell placed over membrane and clamped. Then take the sample with suitable time interval with replacement process. Then calculate the % drug release and plot the drug release curve.[23]

DRUG PROFILE (EUGENOL)[24-26

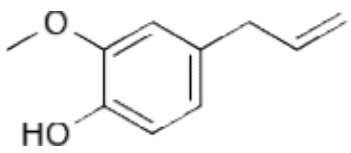

Fig.7 Structure of Eugenol.

Table 1 Chemical, Pharmacokinetic and Pharmacodynamics Profile

IUPAC name	4-Allyl-2-methoxyphenol
Molecular Formula	C10H12O2
Molecular Weight	164.20
Color/Form	Colorless or pale yellow liquid
Odor	Odor of clove
Taste	Spicy
Boiling Point	254 °C (489 °F; 527 K)
Acidity(pK_a)	0.19 at 25 °C
Magnetic susceptibility(χ)	-102.1×10^{-6} cm^3/mol
Vapour pressure	1mm Hg at 78.4°C
Shelf life	10ml: 36 months unopened.
Stability	Darkness & thickness on exposure to air.
Solubilities	Slightly soluble in water, soluble in glacial acetic acid, 1ml in 2ml 70% alcohol. Aqueous fixed alkali hydroxide solutions, miscible with alcohol, chloroform oils.

USE OF EUGENOL

- Eugenol has been used as an antimicrobial, antispasmodic, antiseptic, analgesic and anti-parasitic agent. Clove oil has been marketed as a dental analgesic and antiseptic, a flavoring agent in food, mouthwashes, and pharmaceutical products, and also as an ingredient in aromatherapy. Eugenol is also used as fragrance and flavoring agent and as an insect repellent.[27]
- Eugenol and its derivatives have been used in medicine as local antiseptic and anesthetic and in perfumeries and flavorings. They are used in the formulation of insect repellents and UV absorbers, analgesics, biocides, and antiseptics.[28]
- Eugenol has also been shown to enhance skin penetration of various drugs. This agent is widely used in agricultural applications to protect foods from microorganisms such as Listeria monocytogenes and Lactobacillus during storage, as a pesticide and fumigant.
- Eugenol has been used to treat skin infections and digestive disorders. Ingested eugenol is also a beneficial antioxidant. In moderate amounts, some reports suggest that excessive doses of undiluted oil can cause symptoms. [29]
- Eugenol and clove oil are generally recognized as safe (GRAS) food additive and have been approved for use in foods and dental products.
- Eugenol is anodyne (an agent that soothes or relives pain) for dental emergencies.
- In the treatment of Acne disease apply the paste of clove powder in honey.
- Eugenol is effective in curing Athlet's foot and nail fungus.
- Eugenol known to possess antibacterial properties and is used in dental creams, tooth pastes, mouth washes and throat sprays to cleanse bacteria. It is also used to relives pain from sore gums and improves over all dental health.

- Eugenol combination with zinc oxide is used for temporary filling cavities.[30]

Pharmacology of Eugenol: Eugenol is used to treatment of acne disease. Also it has antibacterial, antifungal antipyretic, analgesic properties. It is used as desensitizing agent.[31]

Mechanism of action of antibacterial activity: Eugenol which is a spicy, heavy aroma and a pale yellow hue. It is found to be toxic for a wide range of bacteria, including the bacteria of acne that is Staphylococcus aureus and Propionibacterium acnes.

The analgesic and antiseptic properties of eugenol gel can treat the disease acne. The gel when applied to the skin can drawn out skin impurities and also reduces the pain caused by cystic areas.
In other word the eugenol is binds to microbial membrane, membrane is damage due to disintegration of lipid and prevention of albumin synthesis and release of proteins and nucleic acid on cell lysis.

Mechanism of action of analgesic activity: Analgesic activity of eugenol can be credited to its ion channel blocking properties. Eugenol blocks Ca^{++} currents in trigeminal ganglion (TG) neurons including dental afferent neurons and this inhibition was independent of TRPV1 receptor activation. Eugenol also blocks Na^{+} and K^{+} channels in TG neurons in the same manner as Ca^{++} channels. So, it can be assumed that analgesic effect of eugenol is due to inhibition of Ca^{++} dependent presynaptic release of neurotransmitters as well as inhibition of PGE2 and interleukin 1β synthesis.[32]

Dose: In topical gel preparation 0.75ml eugenol drug are used according to its effect on bacteria.

Side effect

- Eugenol could be allergic and can cause an anaphylactic reaction which includes itching, shortness of breath, and rashes.
- Eugenol as a dental pain reliever is not recommended for everyone. When undiluted clove oil is consumed in large doses it can be hazardous.
- Eugenol may cause sore throat, vomiting, difficulty in breathing, seizures, fluid in the lungs, bleeding disorders and in extreme cases, kidney and liver damage.
- Eugenol may cause an increased bleeding risk.
- Eugenol may cause male infertility.
- Consumption of clove oil may cause liver or kidney damage.
- Eugenol a component of clove oil may cause low blood pressure.
- Eugenol may inhibit estrogen.

POLYMER PROFILE

Carbopol: Carbopol polymers are polymers of acrylic acid cross-linked with poly-alkenyl ethers or di-vinyl glycol. They are produced from primary polymer particles of about 0.2 to 6 micron average diameter.

- **Company name**: Colorcon
- **Chemical name**: Carbopol 934

Structural formula: Structure formula of carbopol 934 given below.

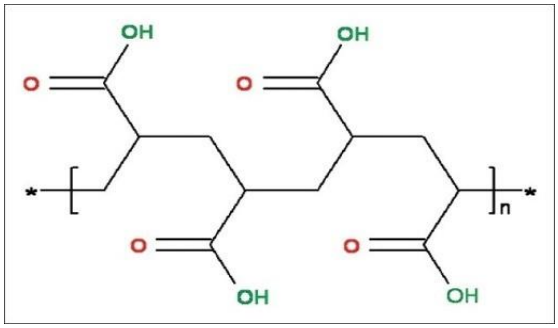

Fig. 8 Structure of carbopol 934

APPLICATION

- **Safe & Effective;** Carbopol 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 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 an excellent 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.
  - → It is widely used in topical, oral, nasal and ophthalmic pharmaceutical formulation.
  - → It is also used as an emulsifier, suspending, stabilizing agent and thickening agent in topical formulation.

It is widely used in cosmetics and food product.
It is soluble in cold water, forming a viscous colloidal solution, practically in soluble in hot water, chloroform, ethanol, and ether, but soluble in mixture of ethanol and dichloromethane, mixture of methanol and dichloromethane and mixture of water and alcohol.

Xanthan gum

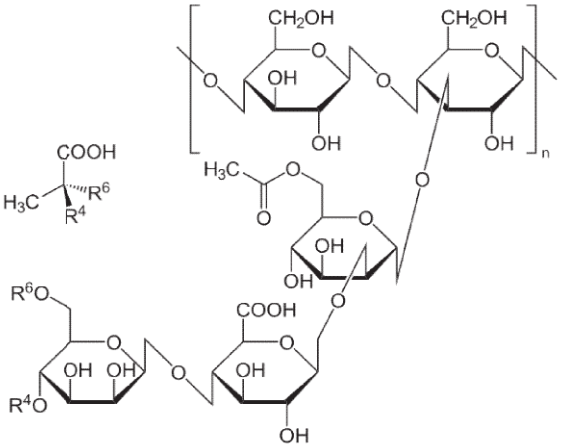

Fig.9 Structure of xanthan gum

Application

- → Xanthan gum is widely used in topical and oral pharmaceutical formulation, s as a suspending and stabilizing agent.
- → It is also used thickening and emulsifying agent.
- → It is practically insoluble in ethanol and ether, soluble in cold and warm water

CONCLUSION

From above review, we can conclude that eugenol gel formulation prepared with different concentrations of carbopol 934 polymer showed acceptable physical property, concerning color, pH, drug content, skin irritation test and antimicrobial activity of formulation. According to 7 days and 15 days stability data the eugenol drug is stable in normal temperature to other condition. In compatibility study data of 7 days and 15 days the eugenol drug was suitable with carbopol 934 in normal temperature comparison to other polymer.

Now day's recent research on ideally drug delivery system which is developing at an enormous rate. Our target at development of drug delivery system with more therapeutic convenience of drug delivery and resulting in secure and potent management of illness. The drug delivery system has become extremely aggressive and rapidly evolving. Now days more developments in drug delivery system are integrated to optimize the ability and cost potencies of the therapy. New grade of pharmaceuticals and biopharmaceuticals (peptides, proteins and DNA- based therapeutics) are stimulates the quick growth of drug delivery technology. The advantage from targeted localized delivery of curative agents is other driving intensity for the market.

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