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DRUG DELIVERY OF EUGENOL AND METHODS THEREOF

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ABSTRACT

Medication Delivery includes the interaction of organization of a medication for accomplishing a helpful impact in humans or animals. The Principal objective is to accomplish a remedial reaction to the medication. Eugenol is the critical phytoconstituent of clove oil, and it is broadly utilized for absence of pain by dental specialists. It displays pharmacological activity on the vast majority of the frameworks. It has cell reinforcement, calming, cardiovascular, pain relieving action. There are numerous difficulties for the plan of eugenol in appropriate medication conveyance frameworks. In this article, there is an outline of Eugenol and its improvement in drug conveyance frameworks that are ideal to accomplish the most extreme reaction in food and drugs.

Keywords: Phytoconstituents, Eugenol, Medications, Drug Development

1.0. INTRODUCTION

It is the major constituent of clove oil and has been used for anesthetic and analgesic activity in dentistry. It is an allyl chain substituted guaiacol, a member of the allylbenzene class of chemical compounds. It is colorless to pale yellow aromatic oil, extracted from certain essential oils especially from clove oil, cinnamon oil, basil, bay leaf. It is present in 80-90% in clove bud oil and 82-88% clove leaf oil. It has pleasant, spicy (clove like) taste. The name of Eugenol is derived from *Eugenia Carophyllata*, which was former Linnean nomenclature term for cloves. The current accepted name is *Syzygium aromaticum* **[1]**.

1.1 Biological Source and Uses

It is a primary compound of essential oil (clove oil). It is extracted from dried flower buds, leaves, barks of the trees *Syzgium aromaticum* and *Eugina carophyllata* (family- Myrtaceae). Commercially available clove oil and cinnamon oil contain highest concentration of eugenol (47-92%) **[2]**.

Eugenol is reported to have anti-inflammatory, insect repellant, anesthetic, antimicrobial, antioxidant, antifungal activities.US FDAhasapprovedeugenol in food asflavoring agent, in dentistry as an analgesic, as a fragrance in personal care product and in aromatherapy. CDSCO has not given the status of drug to Eugenol while Indian Pharmacopoeia has recognized eugenol as Herbal Product **[3]**.

1.2. Chemical Profile of Eugenol

The Structural formula is

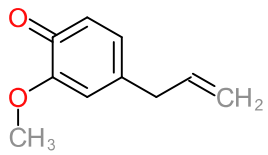

Figure 1: Eugenol Structure

1.3 Chemical Properties

The molecular formula for eugenol is $C_{10}H_{12}O_2$ and molecular weight is 164.20 gm/mol, which is ideal for passive absorption. Eugenol is colorless or pale-yellow liquid having odour of cloves. It is spicy having pungent taste. Its boiling point is 253.2°C at 760 mm Hg and melting point is reported as -9.2° to -9.1°C. The density of Eugenol is 1.0664 gm/ml at 20°C and Water partition coefficient is LogK 2.27, which states that it is poorly water soluble and makes difficult for passive absorption as drugs with Log K < 0 are ideal candidates for the passive absorption **[1]**. The chemical properties says that it can be absorbed passively in the body by increasing its hydrophilicity. Challenges before the researchers arise to make it hydrophilic component before administering into body **[4]**.

2.0 Pharmacological actions of Eugenol

Eugenol has been shown to interrupt action potentials, which may be involved in its anti-pain activity. Research has also shown eugenol to have anti-inflammatory, neuroprotective, antipyretic, antioxidant, antifungal and analgesic properties. Topical application of eugenol is generally safe and also, they are safe when ingested orally **[5]**.

2.1 Mechanism of Action

The exact mechanism of action of eugenol is unknown. However, Studies have reported that it targets alpha estradiol receptor, beta estrogen receptor, androgen receptor and Vanilloid receptor-3. By targeting the estradiol receptor,it prevents accumulation of estradiol by inhibiting it which characterize it as a neuroprotective agent.Antifungal activity of eugenol was studied and it revealed that it is lipophilic and can easily disperse between the fatty acyl chains making up the bilayers of cell membranes. Thus, it modifies the fluidity and permeability of cell membranes, thereby disturbing cell growth and envelope morphogenesis of fungus **[5]**.

2.1 Pharmacokinetics of Eugenol.

Reported data says that the metabolism of eugenol in healthy subjects revealed that it is rapidly absorbed and metabolized following oral administration. It is completely excreted in urine within 24 hours of administration. It was found in urine in the form conjugates and metabolites. Among that 55% consisted of eugenol glucuronide and sulfate. Only 0.1 % of eugenol was not excreted from urine. Epoxide-diol pathway, synthesis of thiophenol and substituted propionic acid, and the migration of double bond were also other routes of its metabolism in humans. Study done by Guenette and cow workers reported the pharmacokinetic parameters using non-compartmental analysis by gavage administration of dose of 40 milligram per kg in rats, plasma half-life was found to be 14 hrs **[6]**.

2.2 Acceptable daily intake.

The Joint WHO expert committee on food additive has published a monograph and specification. The Acceptable Daily Intake of eugenol is 0 to 5 mg/kg **[7]**.

3.0 Challenges in formulation of Eugenol.

It is UV sensitive and may cause irritation or darkening of skin upon exposure to direct sunlight up to four days of application. During nasal administration of eugenol, the concentrated vapours of strong eugenol oil may cause strong irritation, so it is not recommended for nasal administration or direct inhalation. The pharmacokinetic data says that itis quickly absorbedand have long half-life so there is risk of accumulation in body tissues but due to fast metabolism it reaches systemic circulation within a short

period of time and may show side effects. Applying excessive amount of eugenol to large surface of skin or on a broken skin can result in rapid absorption and increase chance of severe side-effects **[8]**.

3.1 Novel Drug Delivery Systems for Eugenol.

Over the past several years, huge development has been made on novel drug delivery systems for plant actives and extracts. Novel herbal formulations like polymeric nanoparticles, nano-capsules, liposomes, nano-emulsions, ethosomes have been reported.

The Novel System should fulfil two requirements

1) Deliver the drug directly to the targeted site.

2) It should channel the active entity of herbal drug.

In phyto-formulation, development of nano dosage form (nanoparticle, nano-capsule, liposome, nano-emulsion, microsphere, microsponges, Insitu Gels) has advantage for herbal drug. These formulations enrich solubility, bioavailability, stability and safeguard physical and chemical degradation **[9]**.

3.2.1 Nanoemulsion Formulation of Eugenol.

Nanoemulsion were developed around 20 years ago. They are mini submicron, ultrafine, fine dispersed emulsion and appear transparent to naked eye. They can be used as novel formulation in cosmetic science, food technology, pharmaceutical formulations **[10]**.

Kamel A. *et al*. formulated eugenolnano emulsion for the anti-fungal studies. The nanoemulsion was formulated using (Eugenol oil 99% & Non-ionic surfactant Tween 80) both were added slowly under gentle stirring until homogenous mixture was formed and further it was sonicated. The nanoemulsion droplets were found to have 2 average diameters 80nm and TEM revealed spherical shape of nanoemulsions. The formulation was evaluated for antifungal activity against *Fusarium oxysporum* sp. Vasinfectum. The study concluded that eugenol oil nano emulsion can be used against *Fusarian oxysporum* fungi **[11]**.

3.2.2 Nanoparticle formulation of Eugenol

Nanoparticle formulation of eugenol gives significant approach to modulate drug release, increase physical stability and protect it from interaction with sun/UV when exposed, decreases volatility and enhances bioavailability. Nano Particles provide sustained release of eugenol in the dermis and thus slow release of eugenol which may not cause side-effects

Sarekha W *et al*. formulated eugenol loaded chitosan nanoparticle. The purpose of this study was formulation of eugenol nanoparticle improving thermal stability. It was prepared by two step method i.e., oil in water emulsion and ionic gelation of chitosan. Tween 60 was added to chitosan solution (1.2% w/v) and mixture was stirred at 50°C 3 minutes. Eugenol was gradually dropped to this stirred mixture and agitation was carried out for 20 minutes. Tripolyphosphate was added to the emulsion for stability. The particle size was 100nm and thermal stability was verified at 155°C and found stable **[12]**.

3.2.3 Liposomal formulation of Eugenol

Liposomes are enclosed spherical vesicles, organized in several concentric phospholipidic bilayers with an internal aqueous phase. Liposome are biodegradable, non-toxic, non-immunogenic, and bio-compatible. They support incorporating natural compounds such as Eugenol by improving solubility and chemical stability.

Carine S, Helene G, *et al*. formulated eugenol loaded liposomes using membrane contractor (600 ml) and pilot plant based on ethanol injection method using Shirasu Porous glass membrane equipment for injection of organic phase to aqueous phase. Liposomes obtained were highly stable, nanometric size and multilamellar. This study was performed to determine if large scale production of eugenol liposome is possible through ethanol injection method and got desirable results as liposome were following all required criterion **[13]**.

3.2.4 Eugenol loaded solid lipid Nanoparticles.

Nanoparticles have many advantages such as increased bioavailability, targeting capability-controlled drug release, improved drug stability and decreased toxicity. They are mostly incorporated in topical drug delivery systems. Solid Lipid Nanoparticles (SLN) provide advantage of delay release through dermal application by accumulation of drug in skin strata which is helpful in various skin disease such as acne, eczema and fungal infection. Poor viscosity of SLN make it ideal candidate for topical application.

Abdul Mohsen H *et al*. formulated eugenol solid lipid nanoparticle for anti-inflammatory effect. Eugenol incorporated lipid nanoparticles were prepared by hot aqueous titration method followed by high pressure homogenization using glycerol monostearate. Phosphatidyl choline was used as co surfactant and polysorbate 80 as surfactant.The nanoeugenol was converted into gel using Carbopol 934 and final

optimized SLN included nanoeugenol (0.25% w/w), Carbopol 934, polysorbate 80 (0.525% w/w), phosphatidyl choline (0.28% w/w). The formulation reported biphasic drug release pattern with burst release within 67.3 minutes followed by sustain release 81.5 hours **[14]**.

3.2.5 Eugenol Microspheres

Microspheres are spherical and free flowing particles having range of average particle size from 1 to 50 microns which consist of organic or synthetic polymers. Microspheres enhances therapeutic efficacy of the drug. The targeted site is delivered with drug and concentration is maintained. Microspheres are able to deliver the drug in target specific site.

Jianping Deng *et al*. formulated Eugenol based polymeric oil absorbent microspheres which is novel type of polymeric microspheres derived from renewable biomass eugenol by effective suspension polymerization approach. Eugenol methacrylate (E-MA) was synthesized using eugenol and methacryloyl chloride. Using E-MA as monomer and crosslinking agent, suspension polymerization with 2,2-azoisobutyronitrile (AIBN) and polyvinyl alcohol as stabilizer resulting in successful preparation of polymeric microspheres. The microspheres were characterized with TEM having diameters 500-800 um and exhibited large oil absorbency in relative high speed. The purpose of this study was reusing the microspheres for at least 5 times and can be taken as versatile platform for preparing more functional polymeric microspheres **[15]**.

3.2.6 Eugenol Microsponges

Microsponges are polymeric delivery systems which aremade of porous microspheres. They are tiny sponge like spherical particles having a large porous surface. They are novel drug delivery systems which enhance stability, reduce side effects and modify release of drug. Microsponge systems are based on microscopic, polymer-based microsphere that can suspend or entrap a wide variety of substances which can be incorporated into gel, cream liquid or powder. The outer surface is porous allowing sustain flow of drug out of sphere.

Vinita C Patole *et al* formulated Eugenol loaded polymeric microsponges using eugenol methacrylate (Eg-MA) later incorporated into in situ gelling system for treatment of periodontis. Eg-MA monomer was synthesized by reacting eugenol with methacryloyl chloride. Microsponges were prepared using suspension polymerization method. Eg-MA was dispersed in deionized

water and introduced into 250 ml RBF with a mechanical stirrer, suspension polymerization with 2,2- azoisobutyronitrile (AIBN) and polyvinyl alcohol as stabilizer resulting in successful preparation of microsponges. The microsponge was incorporated in in-situ gel which was evaluated and characterized. SEM revealed the spherical shape of Eg-MA microsponges, with drug content of 96.38%. The in-situ gel reported release of drug up to 24 h with mucoadhesive strength of 31 N. The formulation reported decrease in tooth mobility and gingivial inflammation in rats **[16]**.

3.2.7 Eugenol Pickering Emulsion

Pickering emulsion is an emulsion that is stabilized only by solid particles (e.g., Solid silica) which adsorb onto the interface between two phases. It was discovered century ago and was named after S.U. Pickering in 1907. If oil and water are mixed and small oil droplets are formed and dispersed throughout the water, the droplets will coalesce to decrease the amount in system. So, if solid particles are added to mixture they will bind to surface of interface and prevent the droplet from coalescing which make emulsion more stable.

Pickering nano-emulsion containing eugenol was formulated by Barbara Horvath. MIC of eugenol was determined on Streptococcus mutants and Pickering emulsion was formulated using Silica nanoparticles and Tween 80 as surfactant, and ethanol as stabilizing agent. The formulation had particle size of 20 nm confirmed by SEM. In vitro study of the formulation reported high effectiveness against Streptococcus biofilms. So, it is concluded that Pickering Nanoemulsions have better performance than conventional gel in dental applications **[17]**.

3.2.8 Eugenol Emulgel

Emulgel is one of the recent technologies in NDDS used topically having characteristics of dual control release i.e., emulsion as well as gel. Emulgels have emerged as one of the interesting topical delivery systems. When drug is incorporated into gel and emulsion they are referred as emulgel.

Om Shelke *et al*. formulated sustained release hydrophobic eugenol emulgel for oral care. The formulation was combination of doxycycline and eugenol. For organic phase eugenol along with cetyl alcohol, mineral oil, emulsifying wax, isopropyl myristate were melted and mixed under stirring at 60^{o} C. Aqueous phase consisted of doxycycline with mixture of EDTA and water and both phases were homogenized for emulsification at 60^{o} C. The bulk was cooled under homogenization till temperature of bulk

reached 32° C and mix the bulk under stirring till temperature of bulk reaches 28° C for emulgel formation. The formulation complied all evaluation parameters and microbial limit tests according to USP. Eugenol and Doxycycline was found to be compatible and combination was effective on nutrient media and had better stability at accelerated storage for 3 months **[18]**.

3.2.9 Eugenol Nanodroplet Gel

Nanodroplet are considered as those nanoemulsion/microemulsion in which droplet size range in nanometer range and later converted to gelling systems. Topical gels possess some advantages such as proper applications, stability and storage.

Shahid H *et al* Nanodroplet gel of eugenol for topical application against inflammation. Formulation was performed using Tween 80 as surfactant and ethanol as co-surfactant mixing with eugenol to obtain nanodroplets (ND). The ND's were converted to gel using carbopol 1%. The NDG were evaluated for rheological properties, in-vitro release, in-vitro permeation. The studies reported formulation had viscous nature and thixotropy to significant level. In-vivo study was performed on rat paw edema induced by carrageenan compared to marketed diclofenac emulgel as control, the study reported to have similar activity of NDG and Marketed Diclofenac emulgel **[19]**.

3.2.10 Eugenol inB-cyclodextrin inclusion complex.

Complexation with beta cyclodextrins (b-CD) improves aqueous solubility and hence resolves many issues associated with developing and commercializing poorly water-soluble drugs. Formation of inclusion complex can be confirmed by DSC, FTIR, XRD and SEM study.Part of molecules which are hydrophobic and can fit into cavity of host in presence of water are included into host cavity. There are many advantages of complexation such as it enhances solubility, bioavailability, stability and masks taste and odour.

Liang Gong *et al* formulated inclusion complex of eugenol (EG) into B-cyclodextrin (b-CD). The EG-b-CD inclusion complex was prepared by method of saturated aqueous solution. 6.50 mmol of b-CD was dissolved in water at 70° C with continuous stirring for 1 hour, to this solution one equivalent 3.25 mmol ethanol: eugenol mixture was added and stirred for 12 hours at 60°C. Later the solution was water evaporated by vacuum and dried at 60°C for 24 hours to obtain product. The formulation was characterized using NMR and reported significant results. Anti-fungal activities of formulation were

evaluated on litchi fruit, the colony growth on litchi reduced after exposure on b-cyclodextrin. The purpose of this study was to preserve the fruits post harvesting **[20]**.

3.2.11 Eugenol Electrospun fibers

Electrospun fibers and fibrous mats have wide application in variety of fields ranging from air and water filtration to biomedical and energy applications. Nanofibers are formulated by electrospinning process. Electrospun nanofibers have many advantages such as diverse chemical composition, easily adjustable structure, high porosity, high surface area which enables it in broad application in biomedical field.

Kourosh Semnani *et al*. formulated antifungal eugenol loaded electrospun PAN (polyacrylonitrile powder) nanofiber mats. Antifungal activity of eugenol was determined against candida albicans. PAN polymer solution was prepared using DMSO, eugenol was added to this mixture before electrospinning. Electrospinning was done with 22-gauge needle tip and voltage 18kV, the feeding rate of polymer solution was 0.35 ml/hr. Characterization of nanofibers was done by SEM, tensile tester. Average diameter of nanoparticles was reported 179-218 nm. Purpose of this study was to treat cutaneous mucocutaneous candidiasis in high-risk patient and in wound dressing **[21]**.

3.2.11 Eugenol in-Situ Gels

The 'in situ gel' is emerging as one of the best novel drug delivery systems, it helps for the sustained and controlled release of drug by its characteristic feature of 'sol to gel' transitional behavior. In situ gelling system is aformulation that is in solution form before entering body and will change to gel for after administration under various physiological conditions. Various polymers are used for In situ gel formation. Mechanism of gel formation involve chemical and physical mechanism. Physical mechanism consists of swelling and diffusion while Chemical mechanism consist of ionic cross linking and enzymatic cross linking. In situ gel reduces the dosage frequency by controlled and sustained release of drug and toxicity of drug.

Suwanne Panomsuk formulated eugenol in-situ gel for buccal mucoadhesion in oral application as antimicrobial, antifungal agents. Insitu gels were formulated using 20% Poloxamer 407 and eugenol was incorporated into polymer as active agent and evaluated for physico-chemical and mucoadhesive properties. Mucoadhesive property was studied on porcine buccal mucosa. Formulation reported good and clear appearance with pH value 5.2 and gelling time reported was 15 minutes on artificial

saliva. The study concluded that eugenol in situ gel is ideal for oral care applications **[22]**.

3.2.12 Muco-adhesive delivery systems for eugenol

Among the available various routes of drug delivery, oral route is mostly preferred by the patient. Mucoadhesion or delivery to the buccal cavity offers a large number of advantages such as bypass first pass metabolism and avoidance of pre-systemic elimination makes attractive factor for buccal delivery. The buccal mucosa has rich blood supply and it is relatively permeable.

Bhimrao K Jadhav formulated Mucoadhesive tablets containing eugenol for treatment of periodontal diseases. The purpose of this study was to introduce eugenol as antibacterial and in analgesic treatment. For the tablets mixtures of hydroxypropyl methylcellulose (HPMC) and Carbopol 934 P in ratio 1:2 was taken and eugenol was incorporated into same layer. Backing membranes were composed of magnesium stearate and physical polymers. Formulation reported controlled release mucoadhesion for 8 hours and release study indicates that carbopol increase release rate and HPMC decrease the release rate of eugenol. The release kinetics of eugenol in vitro correlates with the in-vivo results **[23]**.

4.0 CONCLUSION

Eugenol has potential therapeutic activities against some disease as well as preventing some disease. But, low solubility, high volatility and side effects have limited its use in medicinal application. Various novel drug delivery approach has been able to increase its chemical stability in various factors such as air, moisture, light and prevent degradation. In addition, novel systems ensure safer handling and retains volatile ingredients and better taste masking. Novel systems have controlled release ability to deliver the drug which reduces multiple use of drug and thus, reducing side effects. Various formulations have ability to improve solubility by reducing hydrophobicity and enhancing bioavailability and efficacy.

Nanoencapsulation, nanoparticles, micro and nanoemulsions, liposomes solid lipid nanoparticles, emulgels, b-cyclodextrin inclusion complexes, electrospun fibers, microsponges, In situ gels represent a promising strategy to overcome eugenol limitations, lowering its dose and long-term safety which makes it ideal in medicinal uses.

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