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A REVIEW ON THYMOL ENCAPSULATION AND ITS CONTROLLED RELEASE THROUGH BIODEGRADABLE POLYMER SHELLS

Yashawant P. Bhalerao [1] and Shrikant J. Wagh [*2]

Gujarat Technological University [1], Ahmedabad - 382424, Gujarat, India.
Gujarat Power Engineering and Research Institute [2], Mehsana - 384460, Gujarat, India.

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Correspondence to Author:
Shrikant J. Wagh

Gujarat Power Engineering and Research Institute, Mehsana - 384460, Gujarat, India.

E-mail: sjwagh@gmail.com

ABSTRACT: Encapsulation of thymol is important for its volatile nature, taste, and antispasmodic, antioxidant, antimicrobial, anticancer and anti-inflammatory properties. This review provides a summary of thymol encapsulation in different biodegradable polymers along with the methods of encapsulation and control release in various parts of the body. Biodegradability of shell material along with its health compatibility and the half life of the core material and knowledge of microstructure are some of the main issues that must be addressed while studying encapsulation of Pharmaceutically Active Ingredients (PAI). Different biodegradable polymers used for the encapsulation of thymol are xanthum gum, poly vinyl alcohol (PVA), gelatine, starch, sodium alginate and ethyl cellulose. Preparative conditions, such as concentration ratios, temperature, stirring speed, and nature of solvent used, have deterministic effect on the polymer shell formed around the core material. Purposes for encapsulation of PAI may be numerous, such as controlled release, targeted controlled release, protection/preservation, economic utilization, convenient packaging, and clever option for storage, easy portability and formulation, modification/ hiding undesirable property such as taste, odour and touch. Encapsulation of thymol and its controlled and targeted release *in-vitro* and *in-vivo* is discussed.

INTRODUCTION: Biodegradability of shell material along with its health compatibility and the half life of the core material and knowledge of microstructure are some of the main issues that must be addressed while studying encapsulation of Pharmaceutically Active Ingredients (PAI). Formulation is the process in which different chemical substances *i.e.* active chemical substances in core and shell materials will together produce a medical compound or medical drug.

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Microencapsulation comes as an important protection, storage technique, and controlled release tool for several PAI, food, cosmetic and other medical products. Volatile nature, high reactivity, and low shelf life of core material are some of the reasons prompting to undertake the process of encapsulation. The encapsulation of essential ingredients in core-shell or matrix particles has been investigated for various reasons, *e.g.* protection from oxidative decomposition and evaporation, odour masking or merely to act as support to ensure controlled release.

In order to adapt for different types of active agents and shell materials different microencapsulation methods have been developed, generating particles with a variable shell thicknesses, range of sizes and

permeability, providing a tool to modify the release rate of the active principle [1]. Preparative conditions such as concentration ratios, temperature, stirring speed, and nature of solvent used have deterministic effect on the polymer shell formed around the core material. Thus the final objective of encapsulation is controlled release. But it (encapsulation) can be engineered according to the need. Microencapsulation can promote pharmaceutical base products by introducing innovation, added functional properties and thus added value. In this context it is important to develop novel processes, or optimize existing ones to microencapsulate PAI of interest for pharmaceutical industry, thus contributing towards innovative and added value products creation, in response to human needs and desires.

Methods of Encapsulation and Morphologies of Shells: A microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. The diameters of most microcapsules are in the range between micrometers and millimeters [2]. Microencapsulation is the capsulation of small particle or liquid droplets within a thin film [3]. Typically, the lowest particle size of microcapsules is 1μm and the largest size is 1 mm. Microcapsules consist of a core and a wall (or shell). The structure of the core can be a spherical or irregular particle, a solid suspension to a liquid phase, solid matrix, dispersed solid and aggregates of solids or liquid forms. Purposes for encapsulation of PAI may be numerous, such as controlled release, targeted controlled release, protection / preservation, economic utilization, convenient packaging, and clever option for storage, easy portability and formulation, modification / hiding undesirable property such as taste, odor, and touch. The encapsulated agent can be released by various driving mechanisms, for example, mechanical, temperature, diffusion, pH, biodegradation and dissolution [4].

In microencapsulation, several methods have been used for microcapsule production, in order to be adapted to different types of core and shell materials, as well as, to generate particles with various sizes, shell thickness and permeability, thus adjusting the release rate of the active principle. Broadly the methods are divided into chemical and physical methods. The latter one can be subdivided into physico-chemical and physico-mechanical techniques as listed in **Table 1**.

These techniques are widely used for microencapsulation of several pharmaceuticals. Among microencapsulation techniques, spray drying, spray-congealing, coacervation, fluidized bed, solvent evaporation, phase separation and pan coating are widely used. Methods to be used can be varied depending on the physical nature of the core material to be encapsulated.

TABLE 1: DIFFERENT TECHNIQUES USED FOR MICROENCAPSULATION [5]

Chemical processes	Physical processes	
	Physico-chemical	Physico-mechanical
Suspension, emulsion, dispersion or precipitation polymerization	Coacervation	Spray-drying
Polycondensation	Layer-by-layer(L-B-L) assembly	Multiple nozzle spraying
	Sol-gel encapsulation	Fluid-bed coating
	Supercritical CO_2-assisted microencapsulation	Centrifugal techniques
		Vacuum encapsulation
		Electrostatic encapsulation

On the basis of the size or morphology, microcapsules can be classified into three basic categories as mono-core (also called single-core or reservoir type), poly-core (also called multiple-core) and matrix types **Fig. 1**. Mono-core microcapsules have a single hollow chamber within the capsule; Poly-core microcapsules have a number of different sized chambers within the shell; and matrix type is a micro particle having active compounds capsulated within the shell material. However, the morphology of the internal structure of microparticles depends mostly on the selected shell materials and the microencapsulation methods employed [6].

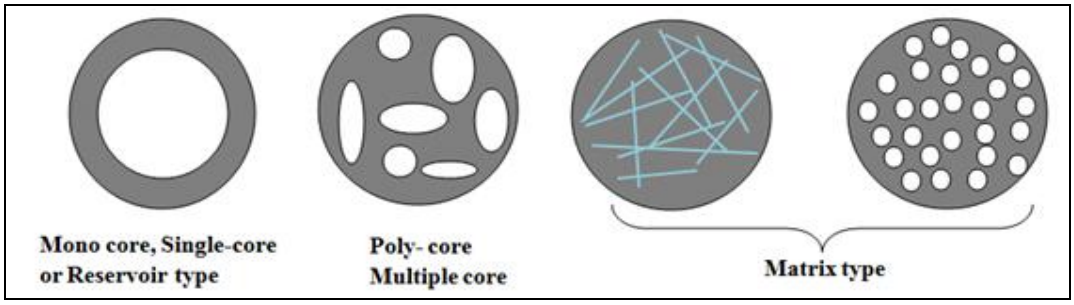

FIG. 1: MORPHOLOGY OF MICROCAPSULES

Many packaging methods are based on the first drops of the core material (gas, liquid or powder form) and are surrounded by carriers in a gaseous or liquid phase by applying different physico chemical methods [6] **Table 2**.

TABLE 2: OVERVIEW OF COMMON MICROENCAPSULATION PROCESSES [6]

Technology	Process steps	Morphology	Load (%)	Particle size (µm)	(Core) and shell
Spray-drying	The spraying of the active ingredient is usually dried out by dissolving, emulsifying or dispersing the active ingredient in an aqueous solution of the carrier material and then by atomization and spraying the mixture in a heated chamber	Matrix	5-50	10-400	(Food, aroma) coated with natural gums (gum arabic, alginates, carrageenans, *etc*.), proteins (dairy proteins, soy proteins, gelatin, *etc*.), carbohydrates (maltodextrins and cellulose derivatives) and/or lipids (waxes, emulsifiers) [7]
Fluid bed coating	The powder particles are suspended by an air stream. Coating is applied onto powder particles and sprayed with an atomized coating material, With time; each particle will be gradually covered every time it is in the spraying zone	Reservoir	5-50	5-5,000	(Food and pharmaceutical products) coating material might be an aqueous solution of cellulose derivatives, dextrins, proteins, gums and/or starch derivatives [8]
Spray-chilling/ cooling	Active agent soluble in the lipids, or present as dry particles in aqueous emulsions. Firstly, droplets of molten lipids are atomized into a chilled chamber (*e.g. via* nozzle, spinning disk or (Centrifugal) co-extrusion), which results in solidification of the lipids and finally their recovery as fine particles	Matrix	10-20	20-200	(Lipid, iron sulphate, vitamins, minerals, acidulants, enzymes and probiotics) it is fat based, and lipid carriers such as wax and oil (*e.g.* palm oil, beeswax, cocoa butter, and kernel oil) can be used [9]
Emulsification	The emulsion is kinetically known as a thermodynamically stable two-phase system and eventually is separated from the aqueous phase. Proper formulation design of both phases and the interface, including choice of ingredients like emulsifiers, might prevent that. Emulsions are commonly made under high shear with, *e.g*., homogenizer, colloid mill, high shear mixer, or stirred vessel	Matrix	1-100	0.2-5,000	(Active substance, drug, pharmaceutical products) in Poly (D, L-lactic acid) (PLA) and poly (D,L-lactic-co-glycolic acid) (PLGA) [10]

	preferably equipped with baffles under shear				
Preparation of emulsions with multilayer	The layer around the "main" emulsion with the ionic emulsifier can be formed by adsorption of the oppositely loaded polyelectrolyte to form a "secondary" emulsion having two-layer interfaces	Reservoir	1-90	0.2-5,000	Emulsions with multilayers composed of b-lactoglobulin -i-carrageenan,b-lactoglobulin-pectin, or sodium dodecyl sulfate (SDS)-chitosan-pectin [11]
Coacervation	The coacervates are converted to a polymer-rich phase (known as a coacervate) and a polymer-poor phase via a liquid-liquid phase separation mechanism of an aqueous solution. According to the number of polymer types present, the process can be identified as simple coacervation when only one type of polymer is involved or complex coacervation when two or more types of polymers of opposite ionic charges are present	Reservoir	40-90	10-800	Citrus oil, vegetable oils, and vitamin A - requires a hydrophilic coating, such as gelatine or gelatine-gum acacia [12]
Preparation of microspheres *via* extrusion or dropping	microbeads consist of a biopolymer gel network encapsulating an active substance called as microspheres. The microspheres are commonly prepared in the presence of the active; butpost loading of blank microspheres containing oil droplets with, *e.g.* aroma is alsoan option	Matrix	20-50	200-5,000	(active agent, such as oil droplets containing aroma, cells, probiotics, yeast, or enzymes) Calcium-alginate gel [13]
Preparation of microspheres *via* emulsification	By adding calcium chloride to an emulsion of water droplets of an alginate solution and vegetable oil. These results in the “break-up” of the emulsion and micro beads are formed by the gelation of the alginate droplets or as alginate calcium (in the form insoluble, such as calcium carbonate) can be present in water emulsion	Matrix	20-50	10-1,000	(Vegetable oil) chitosan, gelatine [14]
Co-extrusion	Coextrusion is an extrusion technology that uses a multi-fluid concentric nozzle that can be fixed, rotating or vibrating; it can be used to prepare spherical microspheres having a hydrophobic drug nucleus and a hydrophilic or hydrophobic shell produced by interfacial gelation	Reservoir	70-90	150-8,000	(Aroma, fish oil, vitamins, freeze-dried probiotics dispersed in oil) calcium-alginate or potassium-carrageenan [15]
Inclusion complexation	Inclusion complexes are formed by trapping or inserting the non-polar region of a molecule into the cavity of another molecule	Molecular inclusion	5-15	0.001-0.01	(b-cyclodextrin) chewing gum, potato, cereal, flour or starch based snacks, and in water-based flavoured drinks and (lipids) amylase [16]
Liposome entrapment	When the (phospho) lipid form is dispersed in the aqueous medium	Various	5–50	10-1,000	Liposomes consist of at least one closed vesicle

	and is found to be exposed to high shear rates, for example using micro-fluidization or a colloid mill. The mechanism underlying liposome formation is a hydrophobic-hydrophobic interaction between phospholipids and water molecules				composed of bilayer membranes which are made of lipid molecules, such as phospholipids (lecithin) and cholesterol [17]
Encapsulation by rapid expansion of supercritical fluid (RESS)	When the supercritical fluid is released through a small nozzle, the sudden pressure drop causes the evaporation of the supercritical fluid or of the transformation into solvent. A solute or inflated envelope is dispersed on the active agent dispersed in the supercritical fluid	Matrix	20-50	10-400	(Proteins or volatile flavours) cellulose, hydroxypropyl methylcellulose [18]
Freeze or vacuum drying	The active ingredient and the carrier dissolved in water can be lyophilized to produce a non-shrinkable porous structure. First, the sample is frozen at temperatures between -90 to -40°C and then dried by direct sublimation at low pressure and at reduced temperature (-90 to -20 °C). After drying, the resulting fragile pin can be broken into smaller pieces if necessary, for example by grinding	Matrix	Various	20-5,000	cryoprotectants (like 10% milk proteins, 30% maltodextrinor 10% disaccharides) may help to stabilize sensitive activeagent like probiotics sensitive encapsulates like liposomes [19]
Interfacial polycondensation	Interfacial polycondensation (IP) is a technique of step polymerization by which a polymer product is obtained under ambient conditions of temperature and pressure, and with less stringent needs of monomer purity than in conventional (homogeneous) step polymerization processes. The technique delivers a product in different forms such as encapsulated active principles, thin films and membranes for several applications, with minimal post-processing	Mono core	various	2-25	Polyurethanes, polyamides, polyureas, polysulfonamides and polyphenyl esters [20]

Encapsulation of Thymol: Nieddu *et al*., (2014) have evaluated encapsulation of thymol in a shell made of cyclodextrin (CD) and a copolymer based on dimethyl aminoethyl methacrylate (DMAEMA). The purpose of encapsulation was to control powderisation, solubilisation, and taste-masking properties. The thymol-beta cyclodextrin complex was prepared by co-precipitation and sealed-heating methods. This work demonstrates that the unpleasant organoleptic properties of thymol can be masked by including thymol in formulation based on cyclodextrin and containing Eudragit® EPO; this formulation can be added to feed ingredients of a standard diet.

Sealed-heated products were obtained by sealing physical mixtures of thymol and beta-CD (1.28 or 2.42 g corresponding to 0.15g of thymol) in a 10 ml glass ampoule where the powder was wet with 1 ml of acidic medium (pH- 5.0) and then heated at 28 ± 2 ºC for 24 h. The inclusion complex prepared by sealed-heating, using a 1:1 molar ratio between two components thymol and beta-CD, is able to increase the dissolution rate of thymol, which

dissolves slowly in Gastro-Intestinal (GI) simulated fluid; this effect is due to the well-known effect of beta-CD acting as a solubilizer of substances that are poorly water soluble. *In-vivo* studies were performed. Sealed-heating is a suitable method for including thymol in beta cyclodextrin with a good loading efficiency; thymol volatility control is achieved by mixing the complex with the DMAEMA copolymer. Beta- cyclodextrin accelerates the *in-vivo* thymol absorption rate compared with the free drug; the thymol half life is still long [21].

Rassua *et al*., (2014) reveal the encapsulation of thymol by using different biodegradable polymers for taste masking effect and to increase its palatability along with two formulations for systemic and local delivery of herbal drug as adjuvant or substitute to current medications to prevent and treat several human and animal infections. Encapsulation of thymol carried out by methylcellulose or hydroxypropyl methylcellulose phthalate (HPMCP) both are natural polymers. Microspheres were prepared by spray drying technique. The paper reveals release characteristics of the thymol from two different polymers in case of encapsulation by methylcellulose. It is seen that the half life period decreases but its bioavailability increases drastically compared to encapsulation in HPMCP. Hence, it is proposed for thymol in low doses form for systematic administration, and in other case, for local treatment of intestinal infec-tions because of very limited absorption rate [22].

Kohlert *et al*., (2002) investigated the terminal elimination phase set in after 10 to 12 h, and thymol could be detected up to an average of 38 hours in human plasma. Elimination half life was determined to be 10.2 h. In the study of systemic availability and the pharmacokinetics of thymol after oral application to humans, no thymol could be detected in plasma or urine. However, the metabolites thymolsulfate and thymol glucuronide were found in urine [23].

Ulloa *et al.*, (2017) prepared microcapsule emulsions by emulsion of oil (O / W) in various concentrations (10, 20% for maltodextrin (MD) and 2, 5% for soy proteins (SP). Obtained microencapsulation efficiency are 99.95% for MD and from 93.1 to 100% for SP, with average diameters of microcapsules from 17 to 27.5 and from 18.8 to 38 µm, respectively. The release of microencapsulated antimicrobial agents (AM) (thymol and carvacrol) from two encapsulation matrices [(MD) and (SP)] were evaluated for possible use in coatings for food packaging. The release rate with 20% MD-thymol [20MD-T] is faster than 10% MD-thymol [10MD-T] Similar results were obtained for carvacrol with the same MD concentration [24].

Cevallos *et al*., (2010) synthesised thymol and cinnamaldehyde inclusion complexes with β-cyclodextrin (b-CD) upon mixing the components in aqueous media and subsequent freeze-drying. Inclusion complexes of thymol and cinnamaldehyde (guest molecules) were prepared by the co-precipitation method.

The work investigated the relationship between the sorption characteristics of b-CDs and complexes formed with thymol and cinnamaldehyde and their release. The complexes were obtained by co-precipitation, filtered, freeze dried, and stored at constant Relative Volatility (RH) in evacuated chambers (22% - 97%) at 25 ºC. The release of encapsulated compound is determined with various techniques; the result showed that the inclusion complexes thymol- β-CD and cinnamaldehyde-b-CD remain stable up to 75% RH during long storage times. In fact, the guests released from the β- CD complexes were detectable in the region of the water adsorption isotherm at which a sharp increase of water content occurred (84% RH). The release of guest molecules was thus governed by the shape of the water sorption isotherm [25].

Shrikant *et al*., (2018) successfully entrapped Thymol in the biodegradable polymer ethyl cellulose by solvent diffusion and nanoprecipitation method. Drug release from prepared polymer matrix was observed slowly in *in-vitro* release profile up to 10 h. Both methods are suitable for the nano particle preparation. No chemical interaction was found in FTIR study and particles obtained are spherical and distinct in nature. Comparison of two methods showed that nanoprecipitation method gives better encapsulation efficiency results while particles prepared by solvent diffusion method gives the more controlled action in *in-vitro* release. Formulation shows maximum 98% drug release in

10 h. Thymol loaded ethyl cellulose microparticles were successfully prepared by solvent diffusion as well as nanoprecipitation method without any incompatibility. This study observed that nano-precipitation method gives quite better results than the solvent diffusion method and seems to be promising for sustained delivery of Thymol [26].

Controlled Release of Thymol: Martin *et al*., (2012) have studied the release behaviour of thymol and p-cymene used as core materials through Poly Lactic Alcohol (PLA) microcapsules. The microcapsules were obtained by a coacervation process. The results have shown that the release of thymol and p-cymene is faster in the first hour keeping controlled release of thymol almost constant in the subsequent days. The release of oils from the PLA microcapsules can be explained by a diffusion mechanism. The diffusion coefficient in the first hour of release was 1.99×10^{-16} m^2/s for thymol and 4.34×10^{-16} m^2/s for p-cymene. However, the diffusion was slower, if considering a period of 5 days with the diffusion coefficients of 3.34×10^{-19} m^2/s for thymol and 3.45×10^{-18} m^2/s for cymene [27].

Milovanovic *et al*., (2016) have investigated that Cellulose Acetate (CA) is a shell material for the controlled release of thymol. The selection of the high pressure process impregnation time allowed the preparation of samples with different thymic contents. Increasing the thymine content in CA (more than 13.65%) resulted in a pronounced change in morphology from swelling to melting, which seemed to change. Also, the increase in thymol impregnation yield over 13.65% Tg of the impregnated CA samples decreased to 29 °C while the crystalline alignment of the CA disappeared.

In the lower impregnation yield samples tested (4.51% and 13.65%) thymol was protected in the CA pores, while in the higher impregnation yield samples (58.90% and 63.84%) thymol also appeared on CA Surface. The release tests showed that the chemical nature of the release medium as well as the thymol content determined the thymol release kinetics of the CA samples. The release time of thymol from CA in water can vary from two days for the samples with lower impregnation yields up to 21 days for the samples with higher impregnation yields.

On the other hand, the results of this study showed that it was possible to release all thymol from the samples within three days with higher impregnation yields when the release medium was simulated gastrointestinal fluids (hydrochloric acid and phosphate buffer salt). These results indicate CA as a promising carrier of thymol with a wide range of potential applications.

Thymol-impregnated CA showed antibacterial activity against 23 bacterial strains, which are the cause of infections with antibiotic-resistant strains in humans. The higher the thymol content in CA, the stronger the antibacterial activity. Thymol-impregnated CA is a new functionalized, solvent-free green material that allows controlled release of this antibacterial substance. The adaptation of the thymic content in CA allows the production of antibacterial material with various possible applications, from food packaging to pharmaceutical or medical devices [28].

Antilisterial Activity of Thymol: Xiao *et al*., (2011) in their work produced spray-dried capsules from zein solutions (Zein is a class of alcohol-soluble storage protein extracted from maize kernels, is available in large quantity, and can be produced as a byproduct of bioethanol industry) with the same concentrations of nisin and thymol but with varying Tween 20. They demonstrate that its non-ionic surfactant can effectively improve antimicrobial functions in food systems. Spray drying is a practical technology for the production of an antimicrobial capsule, which is possessed by a manipulated incorporating surfactant such as tween 20. The addition of intrinsic surfactant impacts microstructure of capsules and release properties of the encapsulated antimicrobials by impacting interactions among capsule constituents. Encapsulation of antimicrobials improved their antilisterial properties in milk [29].

Xue *et al*., (2013) have studied the ability of whey protein isolate (WPI) and maltodextrin (R) to conjugate the thymol nano emulsifier with propylene glycol (PG) to improve the antifungal properties of milk. Thymol was previously dissolved in PG and emulsified in a 7% conjugate solution. Transparent and dispersions with a diameter of <30 m were observed up to 1.5% (w/v) of thymol.

Increased solubility in milk and synergistic activity with propylene glycol. WPI-MD conjugates can be used as new emulsifiers to make thymol-freight emulsions that can be used as preservatives in food applications [30].

Antioxidant Activity of Thymol: Liolios *et al*., (2009) isolated carvacrol, thymol, p-cymene, and c-terpinene by hydro-distillation technique and successfully encapsulated in phosphatidyl choline-based liposomes and the possible improvement of their antioxidant and antimicrobial activities was tested against selected microbial. The antimicrobial properties of the oils were tested by a diffusion technique against four gram positive and four gram negative bacteria and three human pathogenic fungi, as well as the food-borne pathogen, Listeria monocytogenes. In order to explore all possible antagonistic effects between thymol/carvacrol and c-terpinene/carvacrol, the antimicrobial activities of the mixture were also identified before and after liposome encapsulation. All tested compounds presented improved antimicrobial performance after the encapsulation. The antioxidant activity of the mixtures: carvacrol/thymol and carvacrol/c-terpinene was estimated using Differential Scanning Calorimetry (DSC) before and after encapsulation in liposomes [31].

Davoodi *et al*., (2017) reveals the antioxidant capacity and physical properties of potato starch dispersions enriched with polysorbate-thymol micelles. The results showed that potato starch has essential antibacterial action only in the presence of polysorbatetimol but below polysorbate thymol alone. The decrease in antibacterial activities can be attributed to the encapsulation of thymol in the starch chain. Polysorbate thymol caused a decrease in particle size and viscosity and an increase in the zeta potential of the starch dispersions. Polysorbate thymol leads to a decrease in tensile strength, stiffness and swelling, and an increase in the flexibility, solubility and water vapour permeability of starch films, the antioxidant and antibacterial activities of the starch-polysorbate thymol packed and food preservation. Encapsulation of thymol in the dispersion of potato-polysorbate-glycerol-citric acid starch and related molded film. The Starch polysorbate-glycerol-citric acid formulation had very low antioxidant and antibacterial activity, but exhibited strong antioxidant and antibacterial abilities after adding thymol. Ultimately, the improved antioxidant/antibacterial capacities of starch dispersion suggest its potential applications as excipient food or bioactive film preparation [32].

Antimicrobial Activity of Thymol: Chang *et al*., (2012) prepared thyme oil-in-water nanoemulsions (pH 3.5) as potential antimicrobial delivery systems. The nanoemulsions were highly unstable to droplet growth and phase separation, which was attributed to Ostwald ripening due to the relatively high water solubility of thyme oil. Nano stable thyme oil emulsions were tested for antimicrobial performance, as opposed to acid-resistant spoilage yeast, *Zygosaccharomyces bailii* (ZB). Oil phase composition (ripening inhibitor type and concentration) had an appreciable influence on the antimicrobial activity of the thyme oil nano-emulsions. This effect is also dependent on ripening inhibitor types at the same concentration in the lipid phase. Medium Chain Triglycerides (MCT) decreased the antimicrobial efficacy of thyme oil more than corn oil. For instance, when the level of ripening inhibitor in the lipid phase was 70 wt %, the Minimum Inhibitory Concentration (MIC) of thyme oil for nanoemulsions containing corn oil and MCT were 750 and 3000 μg/ml respectively. The results of this review have important implications for the design and use of nanoemulsions as antimicrobial transport systems in the food and non-food industries [33].

Li *et al*., (2012) revealed new antimicrobial films based on colloidal nanoparticles zein coated with sodium caseinate (SC) emulsifier/stabilizer. Zein-SC-nano-loaded thymol were prepared using an anti-solvent technique with a mean particle size and a zeta potential of about 200 ± 20 nm and -40 mV. Films based on zein-SC nanoparticles have higher water resistance properties and superior mechanical barrier SC films and at the same time good stretchability in terms of films. Thymol load may be films based on SC-zein nanoparticles with antimicrobial activity against *Escherichia coli* and *Salmonella*, and DPPH (1, 1-diphenyl-2-picryl-hydrazyl) the radical scavenging activity. Thymol release kinetics of nanoparticle films can be described as a two-phase two steps; namely a first dispersion effect, followed by a sequential slower release and zein nanoparticles SC to control within the given film matrices the possibility of the release

of thymol. In addition, the SC-based zein-format nanoparticle formats film functions have been proposed with or without thymol to reduce the possible relationship between some of the chosen physical properties and the microstructure of the films in a schematic representation [34].

Li *et al*., (2017) prepared various sub-micron-thymol emulsions with a high HLB (hydrophilic-lipophilic balance) surfactant by spontaneous emulsification. The emulsions were then screened for various provocative pathogens to evaluate antimicrobial efficacy. Based on these life tests, sample formulations were tested as washing treatments on lettuce and inverted blueberries with food-based bacterial biofilms. The antimicrobial data show both specific surfactant antagonists and the formulation between thymol and emulsifiers. These emulsions were also effective antimicrobial agents against common and food borne pathogens in the planktonic and biofilm state.

However, the cumulative data suggest the need for brute force screening to characterize potential antagonisms between thymol and the emulsifying agent. Namely, emulsion antimicrobial activity tended to decrease as a function of higher surfactant content. These formulation trends may extend to other chemically related species, such as carvacrol, eugenol and menthol, all of which have poor water solubility. The proposed thymol emulsions offer a unique non-thermal sanitizing method that holds promise as agricultural sprays, washes and aerosols [35].

Antispasmodic Activity of Thymol: Engelbertz *et al.,* (2012) fractionated Thyme fluid extract by Fast Centrifugal Partition Chromatography (FCPC), Low Pressure Liquid Chromatography (LPLC), and High Pressure Liquid Chromatography (HPLC) and compounds isolated were identified by spectroscopic methods. Bioassay testing was done by quantification of antispasmodic activity in the preconstricted rat. Thymol-deprived *Spissum* Extract (SE) had good antispasmodic activity (-37%, related to the maximum contraction). Fractionation guided by bioassay showed that rosmarinic acid and apigenin did not contribute to this effect. Luteolin significantly contributed to anticonvulsant activity (-9%). Thyme extracts have antispasmodic activity, which is at least due to synergistic effects of phenolic volatile oil compounds and the flavone luteolin. Specifications of thyme-containing preparations should refer to this flavone in addition to focusing on the volatile phenols [36].

Anti-inflammatory Activity of Thymol: Riella *et al*., (2012) assess the anti-inflammatory and cicatrizing activities of thymol in rodents, the peritonitis models of inflammation and analysis, followed by the evaluation of myeloperoxidase activity (MPO), total cell counts and histological analysis were used. The animals were treated with thymol (10, 30 and 100 mg/kg), dexamethasone (2 mg/kg) or vehicle (1% Tween 80) (*i.e.* n = 6 /group). To determine the healing potential, thymol was forged in collagen-based dressings and a biological cure test was performed. Thymol significantly reduced edema (100 mg/kg, $p<0.001$), and also the Leukozyteneinstrom, adopted in the injured area (10, 30 and 100 mg/kg) by, as indicated by the honigperoxidase activities ($p<0.001$) Total Cells ($P<0.05$) and histological analysis. Dressed with thymolfilmen on the basis of collagen (COLTHY) they showed significantly greater (7 and 14 days, $p<0.05$) and improved wound healing of granulieractie and improved the density and organization of collagen during wound healing.

The study suggests that thymol is a promising compound that can be used in the treatment of inflammatory processes and wound healing. The pharmacological action of *Lippia gracilis* in folk medicine can be attributed, at least in part, to the presence of thymol in essential oil [37].

Alizadeh *et al*., (2017) revels that among various plants, peppers species are widely used as medicinal plants. Carvacrol (2-methyl-5-(1-methylethyl)-phenol) and Thymol (2-isopropyl-5-methylphenol) are the most important active ingredients of these plants especially *Zataria multiflora* and *Satureja hortensis*. These compounds are monoterpenoid phenols which are chemically very similar and only the position of their hydroxyl group differs. Several researches have documented that carvacrol exhibits various biological activities including but not limited to antioxidant, antimicrobial, antispasmodic, anti-inflammatory, analgesic, immunomodulatory and

chemopreventive activities. Thymol had also beneficial properties including antioxidant, anti-inflammatory, antiseptic, antibacterial, antifungal, antinociceptive, properties. Numerous investigations have been carried out on the properties of these compounds, among which we now refer to a number of them concerning their anti-inflammatory properties and to confirm this study [38].

Future Scope of the Thymol Encapsulation: Microencapsulation of thymol in liposomes, solid microparticles, nano- and microemulsions, and polymeric nanoparticles represents a promising strategy for overcoming thymol's limitations, lowering their dose and increasing long-term safety of thymol. Low dosages of thymol are also formed to be effective to lower its long term effects on various parts of body. Standardization is necessary in terms of purity of product and stability. Microencapsulation formulation can provide an effective alternative for thymol administration in relatively high or low dosage depending upon application.

CONCLUSION: Thymol has potentials for maintaining and promoting health, also preventing and potentially treating some diseases. However, the generally low water solubility and stability as well as the high volatility and side effects associated with their use have limited their use in medicine. Encapsulation is a new approach that has potential applications in medicinal and health research. A practical and alternative method for micro-encapsulation is a sol-gel silica base that takes place at an ambient temperature where the decomposition of compounds is inexpensive because capital investment in production is very low and environmentally friendly. Micro-encapsulation is very useful tool for increasing the chemical stability in the presence of moisture, air, light and high temperatures.

In addition, the microparticles allow easier and safer handling of liquid substances by converting them into solid powders, determining the trapping of volatile substances and masking the taste, prepare controlled release and/or sequential release of various active ingredients, reduce toxic side effects, and improve water solubility of hydrophobic ingredients and increase bio-availability and effectiveness.

The present review not only enlists several works on micro-encapsulation and controlled release of thymol, but also opens up newer pathways for formulation methods for PAIs.

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