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FORMULATION AND CHARACTERIZATION OF HYDROPHILIC OINTMENT BASES WITH CARVACROL AND MAGNOLOL FOR PERIODONTAL APPLICATION

Georgiana Ioana Potra Cicalău[1,2*], Florina Miere (Groza)[1], Amit Kumar Mandal[3], Mariana Ganea[1], Ioana Scrobota[1], Gabriela Ciavoi[1], Claudia Maria Jurca[1,4]

1. *Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania.*
2. *Doctoral School of Biomedical Science, The University of Oradea, 410087, Oradea, Romania.*
3. *Chemical Biology Laboratory, Department of Sericulture, Raiganj University, North Dinajpur, West Bengal, India.*
4. *Department of Genetics, Municipal Clinical Hospital, Dr. Gavril Curteanu, Oradea, Romania.*

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ABSTRACT

Nowadays, bacterial resistance to classical drugs (antibiotics) is increasingly mentioned in the literature. The same situation is presented in the case of bacteria in the oral cavity, so there is an acute need to formulate new preparations with antibacterial or even anti-inflammatory or antioxidant action. The need for these innovative preparations has increased the attention on plant compounds. Thus, this paper brings to the fore hydrogel-type formulations that are strongly compatible with the oral mucosa and contain active substances with antibacterial, anti-inflammatory and antioxidant properties such as magnolol and carvacrol. The hydrogel was designed in four types of formulas that differ in the type of active substance but also in the added polymer concentration. The gels formed were characterized from an organoleptic point of view, stability and rheological properties. The analysis showed that the gels obtained conform to the known standards and have a different viscosity due to the polymer added in different concentrations (0.5% and 1%). Thus, in the future perspective, we want to highlight the influence of the hydrogel base in the release of the active substance respectively to test *in vivo* the antibacterial, anti-inflammatory and antioxidant activity of the designed oral hydrogel.

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Introduction

The global need for effective and safe alternative options for the prevention and treatment of diseases in the oral cavity stems from the increased incidence of disease, increased resistance of periodontopathogenic bacteria to antibiotics currently used, and economic considerations in developing countries [1-4].

Despite the diversity of pharmacological products, they can alter the microbiome of the oral cavity. They can cause unwanted side effects, such as diarrhea, vomiting or tooth pigmentation, sometimes toxic [5-7].

A study by Bidault *et al*. documented bacterial resistance to routine antibiotics (penicillin, cephalosporins, erythromycin, metronidazole) prescribed in treating oral infections [8]. These aspects support the continuous identification of alternative, natural phytotherapeutic drugs isolated from plants used in traditional medicine to replace synthetic chemicals [9, 10].

Herbal extracts have been used for medicinal purposes since ancient times. Researchers are becoming increasingly interested in natural chemicals, essential oils and plant extracts because of their antioxidant characteristics and benefits for human health [11, 12].

Herbal products are advantageous compared to conventional medicines due to their extensive natural activity, advanced safety

Corresponding Author: Georgiana Ioana Potra Cicalău; Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania. E-mail: cicalau.georgiana@yahoo.com.

margin and lower costs [13, 14].

Periodontal disease has been treated with a wide range of treatment approaches over time. To eliminate the microbial load on the periodontium, one of the most prevalent approaches is mechanical treatment and periodontal surgery. However, because periodontal disease is immunogenetically regulated and requires adjuvant therapy, this method is not always appropriate [15]. The increased incidence of marginal periodontitis, the increased resistance of gram-negative bacteria to routine antibiotics, and even their side effects motivate researchers to discover new treatment regimens to prevent and treat periodontal disease [16].

Therefore, the appearance of new phytotherapeutic formulas with bioactive molecules would be beneficial for the minimally invasive, simple and predictable treatment and prophylactic potential in the appearance of marginal periodontitis [17, 18]. In recent years, more and more plant extracts have been scientifically investigated for their effect on the bacterial flora of periodontal disease. Many of these studies are experimental research on rats, as this animal model has histological, immunological, and biochemical mechanisms similar to those found in humans [19-21].

Most medicines have the potential to cause potential side effects, and natural extracts are no exception [22].

In studies on the toxicity of magnolol conducted by the authors Saito *et al*., Magnolol extract was found not to show mutagenic toxicity and genotoxicity [23].

Sarrica *et al*. (2018) found that concentrated magnolia root extract has no mutagenic or genotoxic potential in vivo and in vitro experiments, while an Organization for Economic Cooperation and Development study found that adverse effects occur at concentrations > 240 mg/kg, making it safe for consumption [24].

Human trials have revealed that dietary supplementation with magnolol affects only 1/22 of patients with symptoms including heartburn, thyroid malfunction, or shaking hands. Still, the link between these symptoms and treatment has yet to be established [24-27].

Carvacrol has been approved for food use by the Food and Drug Administration. The Council of Europe has included it in approved chemical flavorings [28]. This extract is also used in the food, spice or pharmaceutical industry [29, 30]. However, various institutions have included *Magnolia Officinalis* in herbal preparations suitable for inclusion in food supplements due to its digestive and rebalancing activity on the oral microbiome [31, 32]. Therefore, when the doses are followed, the two natural extracts, carvacrol and magnolol, can be considered safe, but further research is needed to determine their toxicity when administered in periodontitis and diabetes.

Thus, our paper aims to formulate hydrogels with carvacrol or magnolol. Their evaluation from the point of view of the antimicrobial activity presented in the literature and the evaluation of rheological and organoleptic properties.

Materials and Methods

Preparation of Hydrophilic Ointment Bases with Carvacrol and Magnolol

For application to the gingival canal, four formulas containing carvacrol (5-Isopropyl-2-methylphenol), a phenolic monoterpene present in the essential oil of oregano (Origanum vulgare) and magnolol (2,2′-Bichavicol, were prepared). 5,5′-Diallyl-2,2′-biphenyldiol), a bioactive organic compound classified as lignin isolated from Magnolia Officinalis root. The two natural compounds were chosen to be known to have antimicrobial, anti-inflammatory and antioxidant properties. The formulas differ in the concentration of Carbomer used (0.5% and 1%, respectively).

The periodontal gels with carvacrol and magnolol were prepared in the Laboratory of Pharmaceutical Technology within the Faculty of Pharmacy of the University of Oradea.

The preparation of periodontal gels was performed according to the described formulas **(Tables 1 and 2)**. The concentrations of magnolol and carvacrol were determined by taking into account the minimum inhibitory amount of the two compounds on periodontal pathogens.

For the preparation of the gels, carvacrol and magnolol were purchased from Sigma-Aldrich Chemicals (St. Louis, MO, USA). The proposed gel formulas are presented in **Tables 1 and 2**, and the type and amount of excipients and their role in formulating the gels are also found in the tables.

Table 1. The formula I and Formula II: Hydrogel with magnolol and carbopol 1% and 0.5%.

Component	Concentration Formula I	Concentration Formula II	The role of excipients
Magnolol	0.25 g	0.25 g	Therapeutic agent
Alcohol	5.00 g	5.00 g	Dispersing agent
Propylene glycol	3.00 g	3.00 g	Wetting agent
Carbomer 940	1.00 g	0.50 g	Viscosity enhancing agent
Triethanolamine	1.00 g	0.50 g	Neutralizing agent
Distilled water	Ad 100.00 g	Ad 100.00 g	Vechicle

Table 2. The Formula III and Formula IV: Hydrogel with carvacrol and carbopol 1% and 0.5%.

Component	Concentration Formula III	Concentration Formula IV	The role of excipients
Carvacrol	0.4 g	0.4 g	Therapeutic agent
Alcohol	5.00 g	5.00 g	Dispersing agent
Propylene glycol	3.00 g	3.00 g	Wetting agent
Carbomer 940	1.00 g	0.50 g	Viscosity enhancing agent
Triethanolamine	1.00 g	0.50 g	Neutralizing agent
Distilled water	Ad 100.00 g	Ad 100.00 g	Vechicle

Practically, regardless of the formula initially prepared, all the substances mentioned above were weighed, and the carvacrol or magnolol was solubilized in ethanol 70%. The carbomer was hydrated for 24 hours at room temperature with distilled water. After hydration, add propylene glycol, triethanolamine for neutralization, and then alcohol with the active substance. The whole amount of the mixture is added to 100g of gel by adding water. The obtained mixture is stirred vigorously until gelling **(Figure 1)**.

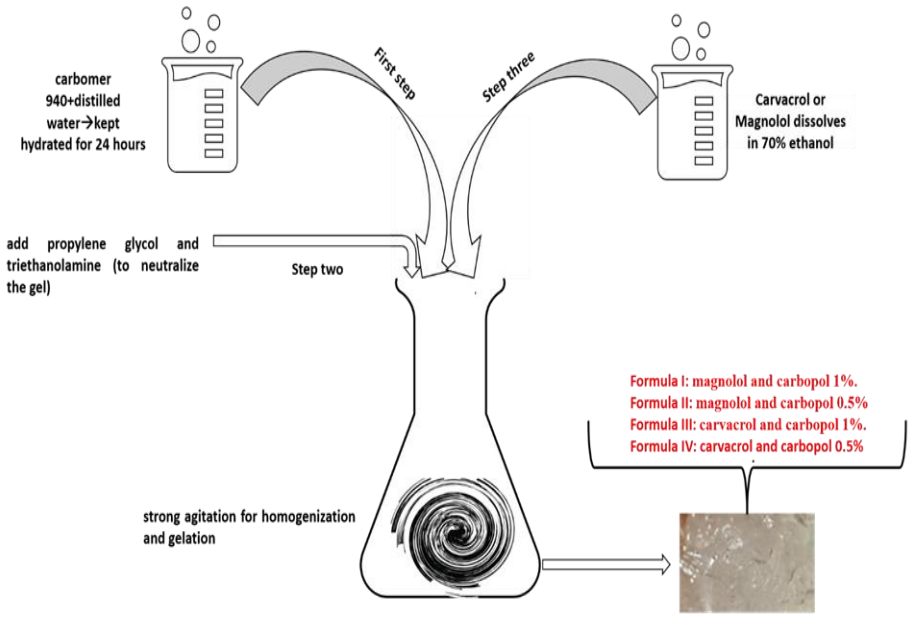

Figure 1. The stages of a gel formulation with the active substance and different concentrations of carbomer.

Quality Control of Bioadhesive Preparations

Organoleptic Control

To assess the efficacy, quality and stability of the preparations over time, a series of determinations characteristic of ointments were performed: organoleptic examination, determination of homogeneity (with 4.5x laboratory magnifying glass), determination of pH (potentiometric method). The determinations were performed on freshly prepared samples and after 30 and 60 days, respectively, to assess their stability.

Rheological Control

To characterize the pharmaco-technical properties of the studied formulas, we performed rheological measurements using a rotary rheometer - DV-III Ultra rotary rheometer (Brookfield Engineering Laboratories, Middleboro, Massachusetts) with a shaft rotation speed of 2 rpm (axis 64). Measurements were performed in triplicate at 22 ± 2°C using RHEOPLUS / 32 V3.10 21003407-33024.

Results and Discussion

The antimicrobial activity of carvacrol and magnolol against periodontal pathogens has been investigated. The studies showed these active substances' minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC). Therefore, to prepare the periodontal hydrogel with carvacrol and magnolol, we used the amounts of carvacrol MIC, and MBC indicated in the literature **(Figure 2)** [21].

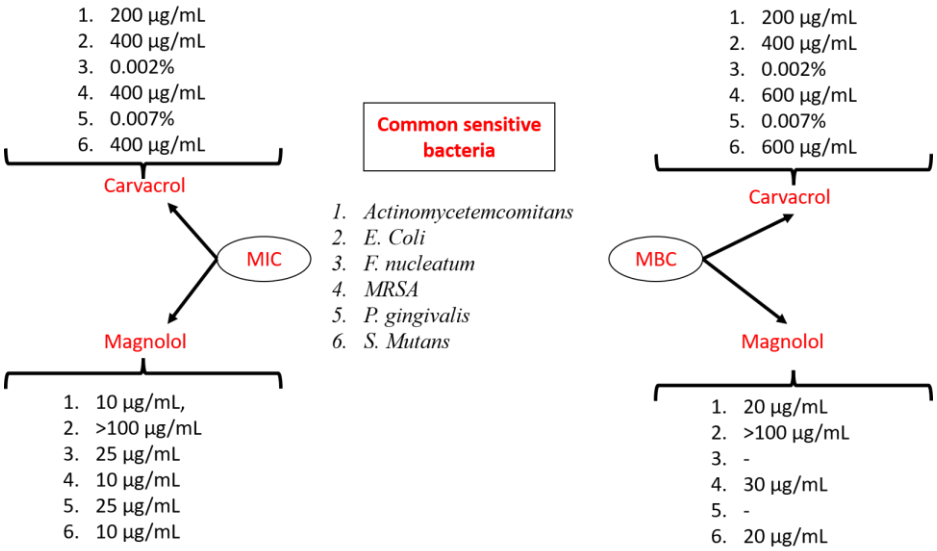

Figure 2. According to the literature, MIC (minimum inhibitory concentration) and MBC (minimum bactericidal concentration) of carvacrol and magnolol.

To properly formulate these bioadhesive preparations, we have considered several practical aspects for preparation [33]. Auxiliary substances play an important role in formulating a pharmaceutical form. Excipients have a decisive influence on the physicochemical properties of the pharmaceutical form, determining its ability to release the drug substance in optimal conditions to achieve the desired therapeutic effect [34].

To ensure good stability and maximum efficiency at the application site, the choice of auxiliary substances and preparation technologies is an important step in obtaining appropriate bioadhesive preparations [35]. Hydrogels adhere to the mucous membranes and allow a good release of active substances [36]. They spread lightly in a thin layer, forming a film that adheres well to the oral mucosa. Hydrophilic gels are obtained from colloidal macromolecules, which have the property of soaking in water by absorption [37].

To formulate preparations with good tolerability to the oral mucosa, we chose excipients suitable for the application site, free of irritating action, and chemically and pharmacologically inert. For this purpose, we used carbopolies as excipients, with or without adjuvants [38, 39].

To obtain the hydrogels, we considered the properties of the components, respectively, and the general methods of preparation of the hydrophilic gels. We considered the consistency (viscosity increasing) agents - carbopole 940 - dispersed in the vehicle using propylene glycol and ethyl alcohol as dispersing agents [40].

Organoleptic Control

Organoleptic control involves determining the preliminary characteristics of the prepared ointments, such as appearance, color, odor and taste. Hydrogels are washable, homogeneous, translucent and colorless. Carbopol 940 gels are homogeneous and transparent, with a characteristic odor and pH of 6.5-7.2. It is observed that the gel with a concentration of 0.5% carbopol 940 has a lower viscosity than the gel with carbopol 940 1%.

The carbopol hydrogels obtained have physiological compatibility with mucous membranes and medicinal substances. They release the active substance well at the application site, penetrate easily through the mucosa and release the active ingredient in their network.

Following the determinations performed to evaluate the organoleptic characteristics of the gels after 30 and 60 days of preparation, respectively, we demonstrated that there are no changes in appearance, consistency or odor **(Table 3)**. Also, we note that the preparations have a pH compatible with the oral mucosa.

Table 3. Organoleptic characteristics of hydrogels.

Formula	Appearance	Consistency	Odor	Color	pH	After 30 days	After 60 days
I	translucent	viscous	characteristic	colorless	6,5-7,2	Unchanged	Unchanged
II	translucent	viscous	characteristic	colorless	6,5-7,2	Unchanged	Unchanged
III	translucent	viscous	characteristic	colorless	6,5-7,2	Unchanged	Unchanged
IV	translucent	viscous	characteristic	colorless	6,5-7,2	Unchanged	Unchanged

Control of Viscosity, Consistency, Adhesion, Firmness and Tensile Properties

We present the average values for the rheological parameters of the hydrogels obtained after three consecutive measurements in **Table 4**.

Table 4. Rheological parameters of hydrogels.

Parameters	Formula I	Formula II	Formula III	Formula IV
Viscosity	5422.6±7.52	5356.2±6.5	5456.23±1.8	5362.4±56.56
Consistency	69.2±1.4	64,2 ± 0.5	71.22±1.6	66.5 ± 1,5
Adherent	4.15±2.3	2.95±1.2	4.20±3.1	3.25±0.9
Firmness	35.9±0.2	29.8±0.7	36.09±1.4	31.3±0.8
Tensile properties	85.0±2.1	65.89±5.65	85.29±5.65	72.23±0.1

Conclusion

Following this study, it can be concluded that the four hydrogel formulas were successfully formulated, which was demonstrated by organoleptic control but also by rheological control.

Major differences were observed in the viscosity of the hydrogel with 0.5% carbomer compared to the one with 1% carbomer, which was more viscous.

according to the data presented, viscosity is an important factor when it comes to the release of the active substance (magnolol or carvacrol)

So, in the future, we want to apply these hydrogels *in vivo* periodontally both to highlight the influence of hydrophilic bases in releasing the active substance and to demonstrate the anti-inflammatory, antioxidant and antibacterial effects of the active substance substances incorporated.

Also, in the future, we want to patent a hydrogel formula with oral application to be used in periodontal diseases.

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