ISSN print: 1224-5984
ISSN online: 2248-3942

Rom Biotechnol Lett. 2023; 28(5): 4142–4148
doi: 10.25083/rbl/28.5/4142.4148

Received for publication, December, 10, 2023
Accepted, March, 10, 2024

Review

Controlled Release of Essential Oils: Mechanisms, Biocompatibility, and Application Perspectives

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Abstract

The efficient control of essential oils (EOs) active compounds release is essential, especially in pharmaceutical formulations, where the stability and bioavailability of active compounds are critical. The use of an encapsulation matrix with specific properties allows for the adjustment of solubility differences, diffusion, and controlled degradation, ensuring optimal and prolonged release of active substances. On the other side, the biocompatibility and safety of materials used for medical applications, the delivery of active pharmaceutical ingredients, the preservation of food and their use in the cosmetics industry are essential factors. The functionalized materials should neither be toxic, nor cause inflammatory or other pathogenic processes. Therefore, a thorough control of the mechanism of release of the active principle, as well as the factors influencing biocompatibility, possible side effects that might occur as a result of biodegradation of the material, must be carried out, and all this is possible by performing biocompatibility tests.

Keywords

Essential oil, wound healing, release mechanisms, biocompatibility, antimicrobial treatments

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Introduction

The efficient control of essential oils (EOs) active compounds release is essential, especially in pharmaceutical formulations, where the stability and bioavailability of active compounds are critical, ensuring optimal and prolonged release of active substances. Understanding the fundamental principles of release mechanisms is essential for the development of advanced drug delivery systems. Drug delivery systems are divided into: classical controlled release systems, intelligent drug delivery systems, systems that modulate drug delivery, in treating certain conditions [1].

These precise strategies have immense potential in optimizing therapies and innovating controlled-release pharmaceutical products [2, 3]. For the evaluation of the release profile of EOs from various matrices that ensure encapsulation, it can be performed through various analytical methods and techniques, such as: UV-Vis after pre-establishing a calibration curve with the essential oil of interest [4, 5, 6], GC-FID [5, 7] and HPLC [8].

Understanding the mass transport mechanisms in the release of phytocompounds is crucial for predicting the drug release kinetics in therapeutic systems. Mathematical models are used to design active ingredient delivery systems and to predict release behavior. These models allow for the measurement of physical parameters and adjustment based on experimental data. Understanding the factors that affect the release rate and dissolution behaviors can influence the efficiency of therapeutic effects as well as biocompatibility. Key mathematical models include zero-order, first-order, Higuchi, Hixson–Crowell, Ritger–Peppas–Kormeyers, Brazel–Peppas, Baker–Lonsdale, Hopfenberg, Weibull, and Peppas–Sahlin [9]. Determining the type of release (Fickian or non-Fickian) based on the mathematical models used in the kinetics of EO release from encapsulation matrices is done by analysing the equations and their parameters. Thus, the Fickian release type (diffusion-based) is applicable for systems with release control based on passive diffusion, while the non-Fickian release type (erosion/dissolution-dependent) is specific to matrices where the release is limited by the dissolution of the matrix (e.g., soluble polymers) [1, 10].

Controlled release mechanisms of EOs

Classical controlled release mechanisms are divided into: fragmentation mechanisms, diffusion and swelling mechanisms, dissolution and erosion mechanisms, release mechanisms under the action of external factors [11]. Fragmentation is a process by which the polymeric structure under the action of external factors undergoes controlled breakage, dispersing it into smaller parts that exhibit the active substance [12]. Diffusion and swelling are synergistic processes, thus, as the rate of swelling increases, an increase in the pore size of the polymer also occurs and thus diffusion of the active principle from the inside of the matrix to the outside is facilitatedn [13]. Synergism can also be observed for dissolution and degradation mechanisms. Therefore, erosion involves the application of a series of processes such as swelling, diffusion and ultimately dissolution of the polymer matrix, and these processes can proceed homogeneously throughout the mass of the material or heterogeneously starting from the surface towards the core [12]. A last mechanism of controlled release involves the application of external factors, pH, temperature, on the chemical structure found in the constitution of the polymer, and the effect produced will consist in the occurrence of swelling and dissolution processes of the material and the elimination of the active principle [11]. Forms of smart drug delivery involve the application of advanced systems that can respond to specific stimuli - pH, temperature, light, various biochemical factors, and extremely small changes in the environment, allowing selective drug release [14]. They are systems based on poly(N-isopropylacrylamide) or polymers derived from it [15]. They are classified into polymers that respond to a single stimulus and polymers that respond to two or more stimuli. In the case of polymers responding to a single stimulus, either exogenous or endogenous, a molecular conformational change is observed through protonation and bond breaking following reaction with water [1]. Endogenous stimuli include factors such as: oxidation-reduction potential, pH, enzyme concentration, and exogenous stimuli include: temperature, electrical pulse, ionizing radiation, light, magnetic field [16]. The release strategies can take two forms: activation of nanocarriers to trigger controlled release only in the presence of a certain stimulus, and modification of the polymer surface electric charge, which based on electrostatic attractions between the positive polymer membrane and the negative target cell membrane of the target cell, internalization of the active principle is achieved [17, 18]. Smart biomaterials have proven to be extremely useful in the case of: lipophilic drugs - to fulfill the therapeutic purpose they need an increase in solubility, short half-life drugs - require repeated doses of application, water soluble drugs - require long on-acting and slow release to achieve the desired therapeutic effect, drugs that need to be delivered to target sites [14].

Biocompatibility and safety

In 1996, Ratner provides a definition of biocompatibility and defines it as the ability of a functionalized or

non-functionalized material to generate a specific reaction in the organism. What could be observed is that there are a number of factors, from the category of physicochemical properties of the polymer, that influence biocompatibility: hydrophilic-hydrophobic character, material surface composition, polymeric material topography, degradation profile and mechanism, wettability and surface free energy [20]. An increased hydrophilic character is known to favor cell adhesion, drug loading, while an increased hydrophobic character reduces cell-cell interaction and prevents bacterial accumulation [21]. Biopolymers, e.g. alginate, should have the highest purity, lowest molecular weight and viscosity to minimize the host immune response that may occur [22]. The smooth titanium surface confers an increase in fibroblast proliferation compared to the rough titanium surface [20, 23]. The incorporated active principle also has a considerable contribution on biocompatibility. Among the factors influencing the biocompatibility of oils are: variable chemical composition, concentration and dose of volatile oil applied, contact time, solubility in solvents, volatility of essential oils. Thus, the terpene and phenolic components of volatile oil can alter the cellular redox state, and the induced effect is dose-dependent, with low concentrations having an antioxidant and reactive oxygen species protective effect, while high concentrations cause membrane permeabilization, establishing a prooxidant effect manifested by damage to mitochondrial proteins and DNA [24]. In the case of carvacrol, thymol and γ-terpinene Aydin et al. in 2005 found that antimutagenic and non-cytotoxic effects are preserved at low concentrations of the active compound, similar effects were also obtained by Palozza et al. in 2004 in the case of carotenoid, in addition, apoptosis-stopping effects were also observed. The solubility of EOs in polar solvents modulates biocompatibility by activating specific mechanisms. It is known that DMSO exhibits cytotoxicity manifested by the appearance of pores at the plasma membrane, contributing to increased cell permeability [27], ethyl alcohol causes an inhibition of cell proliferation by disrupting ATPase functions and inhibiting glycolytic enzymes, and disorganization of transmembrane proteins because of membrane fluidization [28]. All of these effects can be mitigated by their incorporation into controlled-release systems that favor increased bioavailability and preservation of the properties of EOs [29, 30, 31]. Materials designed for medical applications are not only limited to inertia, but include both biofunctionality and biostability [32]. The period of application of the medical device, the type of application, the interaction with the biological environment, as well as the material properties are concepts that need to be constantly analyzed and evaluated [33]. The evaluation of the aforementioned parameters is done by biocompatibility tests that can be performed *in vitro* and *in vivo* (Table 1) [32, 34].

The biodegradation of synthetic polymers is carried out, *in vivo*, by inflammatory cells and involves the simultaneous unfolding of several processes: the onset of oxidative stress by lowering the extracellular pH and intracellular calcium influx, the production of reactive oxygen species (ROS) and radical species by breaking polymer bonds and the appearance of monomers, subsequently oxidation of membrane lipids and utilization of glutathione occurs in this process, if these processes are exacerbated there may be damage to biological tissues, increased cytotoxicity, and ultimately cell death [55, 56, 57, 58, 59].

Biodegradation of natural polymers produces a number of positive and negative effects *in vivo*. The beneficial effects of the use of these polymers, especially glycosaminoglycans, are the establishment of an antioxidant effect, to reduce ROS that could disrupt the oxidoreduction balance [60], improve cell adhesion and proliferation [59]. The negative effects derive from the improper degradation of structural components, for example the extracellular matrix indirectly induces the synthesis of oxidants with chemotactic effect for immune cells, also damage-associated signals favor the increase of free radicals, and ROS [61, 62].

Conclusions

The controlled release of essential oils (EOs) through specialized delivery systems is vital to ensuring their stability, therapeutic efficacy, and safety across pharmaceutical, cosmetic, and food applications. By understanding and tailoring classical and stimulus-responsive release mechanisms—such as fragmentation, diffusion, dissolution, and external factor activation—researchers can fine-tune EO release kinetics to match specific treatment or product requirements. Mathematical modeling plays a key role in predicting and optimizing these release profiles.

Biocompatibility remains an essential consideration for all EO-based formulations. The encapsulation matrix, whether synthetic or naturally derived, must not trigger inflammatory or cytotoxic effects; hence, in vitro and in vivo tests are indispensable. Key parameters—like polymer hydrophilicity, surface composition, degradation profile, and the unique properties of each EO—strongly influence cell viability, genotoxicity, hemocompatibility, and potential allergenicity. These assessments help ensure that the released EO maintains its desired biological activity without causing adverse effects, such as oxidative stress or damage to host tissues.

Table 1. Biocompatibility assessment by *in vitro* and *in vivo* tests

Biocompatibility tests	*In vivo/In vitro* studies	Type of tests	Principle of the method	References
Cytotoxicity (MDA-MB-231, MCF-7 and MCF-12A cell lines)	*In vitro*	MTT assay	Spectrophotometric evaluation of cell viability following enzymatic reduction of tetrazolium salt to formazan	[35, 36]
Cytotoxicity (HepG2 cell line)	*In vitro*	NRU assay	Evaluation of cell integrity and growth spectrophotometrically by lysosome incorporation of bind neutral red	[37, 38]
Cytotoxicity (cell line-derived xenografts)	*In vitro*	LDH assay	Assessment of plasma membrane integrity by extracellular release of lactate dehydrogenase.	[39, 40]
Genotoxicity	*In vitro*	Ames test	Quantification of the mutagenic activity of substances of interest on the bacterial L-histidine operon,	[41]
Genotoxicity	*In vitro*	Comet assay	Electrophoretic quantification of the integrity of the DNA molecule by the appearance or absence of comets.	[42, 43]
Genotoxicity	*In vitro*	Micronucleus test	Microscopic quantification of the number of micronuclei in eukaryotic cells.	[44]
Hemocompatibility (Human, rat, rabbit, mouse blood cells)	*In vitro*	Hemolytic potential	Assessment of the degree of hemoglobin release that may occur when the test substance comes into contact with blood	[45, 46]
Hemocompatibility (Unfractionated heparin, low-molecular-weight heparin; human blood cells)	*In vitro*	Coagulation assay	Quantification over time of the rate of clot formation in the presence of an active substance	[47, 48]
Hemocompatibility (Human blood cells)	*In vitro*	Platelet activation testing	Assessment of platelet functionality by flow cytometry, Light Transmission Aggregometry or ELISA	[49, 50]
Skin test (Mouse skin)	*In vivo*	Irritation (intracutaneous reactivity) testing	Temporal dynamic assessment of skin reactions following subcutaneous injection of the active substance	[51]
Skin test (Guinea pig skin)	*In vivo*	Skin sensitization assay	Temporal dynamics assessment of the allergenic effect induced by the active substance	[52, 53]
Animal models (Mouse model)	*In vivo*	Acute systemic toxicity testing	Evaluation of immediate toxic effects following repeated exposure of animal models to fixed doses of the active substance	[32, 51]
Animal models (Rabbit, sheep, goat, and rat models)	*In vivo*	Implantation tests	Histologic evaluation of localized pathologic effects following implantation of the medical device in the body of the animal model	[54]

Overall, continued interdisciplinary research and collaboration between materials scientists, chemists, biologists, and clinicians will further refine these encapsulation and release strategies. Such efforts will enable more precise, efficient, and safe EO-based products, paving the way for innovative therapeutic solutions and advanced applications in wound healing, antimicrobial treatments, and beyond.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

PN-IV-P7-7.1PED-2024-2232 (43PED/08.01.2025).

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