MULTIPLE EMULSIONS FOR SIMULTANEOUS ACTIVE AGENTS DELIVERY IN A SKIN TOPICAL APPLICATION

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Most antiseptic agents are intended for use on intact skin, e.g. for hand hygiene or skin preparation before any medical procedure. This paper presents multiple emulsion-based antiseptic agents as formulations for application to body surfaces with modified release rates.

Multiple emulsions with a co-encapsulated antiseptic (phenyl salicylate – salol) and an agent preventing microorganism growth (benzoic acid) were formed in a Couette–Taylor flow apparatus. Results confirmed the possibility of the release kinetics modification while two compounds were encapsulated in the internal droplets of emulsions to control the release rates and time of the dose release. The addition of benzoic acid as a second active compound of the encapsulation process in the internal phase of double O1/W/O2 emulsion reduced the time necessary for the total release of salol triggering a two-step release.

Keywords: multiple emulsions, antiseptic agent, simultaneous release, co-encapsulation

1. INTRODUCTION

Drug delivery systems hold an active agent concentration in plasma between the minimum effective concentration and the minimum toxic concentration to achieve the therapeutic effect (Perrie and Rades, 2012; Siegel and Rathbone, 2012; Wilson, 2012). Modified release of an active agent from a drug delivery system includes delayed, sustained, controlled, organ targeted, or cell receptor-specific release (Perrie and Rades, 2012). The modified release is controlled by different mechanisms e.g. diffusion, osmosis, swelling and dissolution, and degradation in different specific formulations of drugs (Lam and Gambari, 2014). Delivery of more than one active agent (drugs, food, vitamins), including targeting, is provided by systems such as nanoparticles, liposomes, nanofibres, and simple emulsions/nanoemulsions and multiple emulsions. An example is a nanoemulsion with vitamin E as the core and two different anticancer drugs: paclitaxel and fluorouracil (Ma et al., 2014) or an immunoemulsion with the anticancer drug (e.g. paclitaxel) and monoclonal antibody (e.g. Herceptin) adsorbed onto the surface (Goldstein et al., 2007). Also, multiple emulsions are used for the co-delivery of encapsulated hydrophilic and hydrophobic substances in the combination therapy. Multiple emulsions are complex dispersed systems of hierarchical structures “drops in a drop”, Fig. 1. Double emulsions are the simplest multiple emulsions that can contain two or even three different active agents in each phase. An example is sodium lactate, spironolactone, and chlorhexidine
digluconate in W/O/W double emulsion or metronidazole with ornidazole in internal and external phases of W/O/W for topical application (Özer et al., 2007; Raynal et al., 1993). The anticancer treatment causes many side effects, including those on the skin and its appendages. Anticancer agents and radiotherapy can induce many dermatological complications e.g., paronychia, skin rash, acne, onycholysis, hyperpigmentation of nail and/or skin, or even wounds. They are often associated with skin swelling, itching, and skin dryness. Some of the changes appear already during the therapy, others just after it is finished and they have a very strong influence on the quality of life for oncological patients (Fabbriocini et al., 2012; Hymes et al., 2006; Priyadarshini et al., 2016; Spałek, 2016). Due to emulsions’ properties, these systems are often used as pharmaceutical or cosmetic topical formulations to provide dermal or transdermal delivery of active substances (Fig. 1), (Otto, 2009). Emulsions are the base to produce moisturizer formulations, which can deliver to the skin various kinds of emollients e.g. isopropyl palmitate, octyl stearate, glyceryl stearate. Moisturizers are very important in skincare. They can be very useful for the treatment of different kinds of dermatitis, because of their properties which allow them to enhance skin hydration and softness, which are the main skin problems for oncological patients (Purnamawati, 2017). Emulsion-based product Biafine is widely used in wound care and treatment of radiation dermatitis (Cohen et al., 2007). Another substance with wound healing and skin condition maintaining properties, which can be contained in the emulsion system, is allantoin. Natural oil-based emulsion with this substance can be used to manage skin reactions induced by radiation (Chan et al., 2012; Chan et al., 2014). Weak and damaged skin ought to be also well protected from other factors, such as solar radiation. Emulsions are also widely used as sunscreen agent carriers. The emulsion system used to prepare these products is essential because it influences sunscreen skin permeation from the formulation (Durand et al., 2009; Montenegro et al., 2008). Most antiseptic agents are intended for use on intact skin, e.g. for hand hygiene or skin preparation before any medical procedure. If the skin is wounded, the application of antiseptic agents requires either a different route of administration or specific formulations. Due to the presence of a protective oil or water phase (depending on the type of O/W/O or W/O/W emulsion), multiple emulsions enable the encapsulation of an antiseptic agent and its release even after its application to the wounded skin. Also, the kinetics of the active agents’ release plays an important role. The release rates and connected release time and dosage may be controlled or modified. The controlled release of the active substance ensures a predictable pattern and constant concentration of the active substance in the blood. The modified release can be further divided into prolonged/sustained, delayed, multi-step, or pulsatile release. The control or modification of the release profiles involves drug delivery systems such as nano/microparticles, polymersomes, liposomes/nanosomes, carbon nanotubes or quantum dots, colloidal drugs, and emulsions, including multiple emulsions (Lam and Gambari, 2014; Siegel and Rathbone, 2012; Wilson, 2012).

![Fig. 1. Multiple emulsions with two encapsulated ingredients for skin conditions caused by anticancer treatment. The molecular structures of salol (phenyl salicylate) and benzoic acid (PubChem CID 8361; PubChem CID 243)](https://journals.pan.pl/cpe)
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The paper concerns O1/W/O2 double emulsions with two different substances for local modified delivery of an antiseptic (phenyl salicylate – salol) and an agent preventing microorganism growth (benzoic acid). The O1/W/O2 double emulsions contain an internal oil phase dispersed as small droplets in the water membrane phase drops (Fig. 1). The water phase separates the internal oil phase from the external phase. The scope of the study covers the preparation of double emulsions with simultaneous co-encapsulation of active ingredients in a Couette–Taylor Flow (CTF) apparatus and analysis of their co-release kinetics. The objective of this study was to determine whether adding a secondary agent (benzoic acid) into the internal droplets of emulsions influences the salol release profiles, and in consequence salol release time. In addition, the release mechanism of co-encapsulated ingredients was investigated and confirmed by an emulsion stability analysis, which included droplet size measurements under different release conditions. The obtained findings may be useful for the design of multiple emulsions with the desired co-release kinetics, which could be used as formulations for skincare management in cancer patients (Fig. 1).

2. MATERIALS AND METHODS

2.1. Materials

O1/W/O2 (1/2/3) double emulsions were prepared from solutions being: internal phase (1), membrane phase (2), and external phase (3). The internal phase was the solution of salol (phenyl salicylate), (Sigma – Aldrich, USA) and benzoic acid (Chempur, Poland) in liquid paraffin (COEL, Poland) at 80°C (1). Concentrations of salol and benzoic acid in the solution that were the internal phase of the emulsions are summarized in Table 1. An aqueous solution containing 15 wt.% of gelatin (POCH, Poland) and 5 wt.% of sucrose (cross-linkers) at 80°C was used as a membrane phase (2). The external phase was liquid paraffin at 20°C (3).

2.2. Preparation of double emulsions with an antiseptic and preventing microorganism growth agents

A one-step emulsification method in a Couette–Taylor flow (CTF) apparatus was used to prepare multiple (double) emulsions with salol as an antiseptic and benzoic acid as an agent preventing microorganism growth. The emulsification method was described in previously published papers (Dluska et al., 2017a; 2017b). The CTF apparatus creates uniform shear flow, a large interfacial area and high mass transfer coefficients, essential for stable emulsion formation (Dluska et al., 2007; Dluska and Hubacz, 2000). In order to improve the quality and stability of double emulsions, preparation conditions were selected based on formerly conducted experiments (Markowska-Radomska and Dluska, 2016; Markowska-Radomska and Dluska, 2012; Dluska and Markowska-Radomska, 2010). The ratio of the volumetric flow rates of phases was: membrane to external 0.15, internal to external 0.5. Each of the liquid phases was separately dosed by peristaltic pumps. The rotational frequency of the inner cylinder was between 1080–2360 rpm. The annular gap width and length in the CTF apparatus were 1.5 mm and 40 cm, while the inner cylinder diameter was 2.5 cm. Table 1 contains a detailed description of emulsion preparation parameters.

Table 1. Characteristics of multiple emulsions with two active ingredients formed in the CTF apparatus

<table>
<thead>
<tr>
<th>Emulsions’ set</th>
<th>ME-1</th>
<th>ME-2A</th>
<th>ME-2B</th>
<th>ME-3A</th>
<th>ME-3B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of salol [%wt.]</td>
<td>9.25</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Concentration of benzoic acid [%wt.] · 10³</td>
<td>2.68</td>
<td>9.09</td>
<td>9.09</td>
<td>2.95</td>
<td>2.91</td>
</tr>
<tr>
<td>Rotational frequency of the inner cylinder in the CTF contactor [rpm]</td>
<td>1622</td>
<td>1622</td>
<td>1802</td>
<td>1622</td>
<td>1802</td>
</tr>
</tbody>
</table>
2.3. Determination of drop size distributions and stability of multiple emulsions

Drop size distributions and mean diameters of emulsion samples were determined by microscopic and image analysis. Microscopic observation set-up consisted of an optical microscope BX-60 Olympus connected to an Olympus SC50 camera: 10–15 microscopic pictures of freshly prepared emulsion samples were captured. Microscopic observations were continued in time intervals during the active agents’ release study. The drop size distributions, the mean diameters (arithmetic, Sauter, and De Brouckere) of the internal and membrane phase drops, the volume fraction of the internal phase droplets in the membrane phase drops and polydispersity index were determined using image analysis with Image Pro Plus 4.5 software. The emulsions were evaluated as stable if the changes in the Sauter mean diameter of drops, after one month of preparation, were less than 15% of the initial mean diameter of drops (after preparation).

2.4. Encapsulation efficiency of salol and benzoic acid

Salol and benzoic acid encapsulation efficiency was calculated as a difference between the concentration of active agent added to the internal phase and its concentration measured in the external oil phase of the emulsion. Samples of the external oil phase were separated from the emulsions by filtering liquid paraffin using hydrophobic syringe filters. Concentrations of the two different encapsulated active agents were measured by HPLC and GC.

2.5. In vitro release study of salol and benzoic acid from double emulsions

Release experiment concerned simultaneously co-release benzoic acid and salol from the internal paraffin drops through the aqueous membrane phase to the external oil phase of double emulsions. Benzoic acid and salol in vitro release experiments were conducted in the stirred glass batch reactor – glass tank dimensions: height – 0.2 m, diameter – 0.1 m; 4 blade turbine impellers: diameter – 0.05 m, blades set at an angle of 45°. Emulsions were stirred under constant rotational frequency of 150 rpm (for ME-1) or 250 rpm (for ME-2A, ME-2B, ME-3A, and ME-3B) at a constant temperature of 37 °C, the volume of the emulsion was 0.976 dm³. The concentration of benzoic acid and salol in the external oil phase of the emulsions over time was examined. Samples of the external oil phase of the emulsions were drawn using the same method as for the encapsulation efficiency study. The release profiles are presented as the cumulative mass of salol released from the emulsion at time t to the continuous external phase, related to a maximum release achieved in a given experiment in an infinite time. Three independent series of experiments were made. In the figures, the results are presented as (mean ± standard deviations (SD)).

2.6. Quantification of benzoic acid by HPLC and salol by GC

2.6.1. Quantification of benzoic acid

HPLC quantitative analysis of benzoic acid was carried out using Agilent 1260 Infinity liquid chromatograph equipped with a UV-DAD detector. The mobile phase was acetonitrile/water 50/50 vol., both solvents were acidified with H₃PO₄ to get a concentration of 0.02 M. The flow rate was 1 cm³/min, detection at 241 nm was applied and injection of 0.025 cm³. The analysis was carried out using a Supelcosil ABZ+ column 150 × 4.6 mm with precolumn 10 × 4.6 mm, thermostated at 60 °C. HPLC grade solvents were used. The samples (in paraffin) were extracted in an ultrasonic bath at 30 °C for 30 min. The samples of exact masses from the range of 200–250 mg were extracted in a 5 cm³ graduated flask, containing 2 cm³ acetonitrile and water added to the mark. Before measurements, extracts were filtered using 0.45 μm PTFE disposable
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filters. The quantification was based on an external standard method. Before every series of measurements, a calibration curve linearity was found in the range of 0.065 μg/cm³ – 1.300 μg/cm³, prepared in eluent ($R^2 > 0.99$). The average efficiency of extraction was 32% (±1%).

2.6.2. Quantification of salol

The quantitative analyses of salol were performed using a GCMS system equipped with a gas chromatograph GC 7890A coupled with mass detector VL MSD 5975C, both from Agilent. A capillary column HP-1701 30 m × 250 μm × 0.25 μm was used, with helium as the carrier at 1 cm³/min. The sample volume was $5 \cdot 10^{-4}$ cm³ at a split value of 1:10 and the injector temperature 200 °C. The temperature program was as follows: from an initial temperature of 50 °C held for 1 min a linear temperature increase of 20 °C/min to 250 °C was applied, which was held for 9 min. For preparing samples HPLC grade solvents were used. The analysis was performed in TIC mode at m/z 10–700. The samples (in paraffin) were extracted in an ultrasonic bath at 30 °C for 15 min. The samples of exact masses from the range of 60–80 mg were extracted in a 10 cm³ graduated flask, containing acetonitrile. Before measurements, extracts were filtered using 0.45 μm PTFE disposable filters. The quantification was based on an external standard method. Before every series of measurements, a calibration curve linearity was found for salol in the range of 0.014 mg/cm³ – 1.560 mg/cm³, prepared in acetonitrile ($R^2 > 0.99$). The average extraction efficiency was 91% (±2%).

3. RESULTS AND DISCUSSION

3.1. Characterization of double emulsions with two active agents and stability study

Multiple emulsions prepared via a one-step emulsification process were characterized based on light microscopy observations and the values of encapsulation efficiency of salol and benzoic acid. Five different sets of double emulsions were taken for more specific analyses to determine drop size distributions and various mean diameters of membrane water phase drops and internal oil phase drops were determined and summarized in Table 2.

Table 2. Characterization of obtained sets of double emulsion

<table>
<thead>
<tr>
<th>Emulsion set</th>
<th>ME-1</th>
<th>ME-2A</th>
<th>ME-2B</th>
<th>ME-3A</th>
<th>ME-3B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ϕ [%]</td>
<td>32.48</td>
<td>27.08</td>
<td>88.14</td>
<td>30.18</td>
<td>71.59</td>
</tr>
<tr>
<td>$D_{10}$ [μm]</td>
<td>45.43</td>
<td>44.50</td>
<td>50.47</td>
<td>46.23</td>
<td>44.37</td>
</tr>
<tr>
<td>$D_{32}$ [μm]</td>
<td>71.89</td>
<td>99.22</td>
<td>68.09</td>
<td>73.74</td>
<td>65.84</td>
</tr>
<tr>
<td>$D_{43}$ [μm]</td>
<td>84.33</td>
<td>119.00</td>
<td>75.36</td>
<td>85.87</td>
<td>76.67</td>
</tr>
<tr>
<td>PDI [-]</td>
<td>1.86</td>
<td>2.67</td>
<td>1.49</td>
<td>1.86</td>
<td>1.73</td>
</tr>
<tr>
<td>$d_{10}$ [μm]</td>
<td>5.25</td>
<td>3.22</td>
<td>9.47</td>
<td>5.01</td>
<td>4.95</td>
</tr>
<tr>
<td>$d_{32}$ [μm]</td>
<td>10.83</td>
<td>8.86</td>
<td>24.91</td>
<td>10.89</td>
<td>10.91</td>
</tr>
<tr>
<td>$d_{43}$ [μm]</td>
<td>13.33</td>
<td>12.36</td>
<td>29.88</td>
<td>14.00</td>
<td>12.90</td>
</tr>
<tr>
<td>PDI [-]</td>
<td>2.54</td>
<td>3.84</td>
<td>3.15</td>
<td>2.80</td>
<td>2.61</td>
</tr>
</tbody>
</table>

Emulsions with less favorable characteristics were emulsions of sets ME-1 and ME-3A (the rotational frequency of the inner cylinder in the CTF apparatus: 1622 rpm) characterized by encapsulation efficiency

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and volume fraction of dispersed phases of about 50%. Multiple emulsions from sets ME-2A, ME-2B, ME-3B were characterized by encapsulation efficiency of around 70–80%. Multiple (double) emulsion ME-3B (the rotational frequency of the inner cylinder in the CTF apparatus: 1802 rpm) was evaluated as the most favorable system: the encapsulation efficiency of both active agents (77%), and the Sauter mean diameter of internal and membrane droplets providing the highest interfacial area. Drop size distributions of the membrane and internal phase of set ME-3B – O1/W/O2 double emulsion are presented in Fig. 2. The obtained results confirmed the stability of emulsions within 30 days after the preparation.

3.2. The simultaneous release of two active agents from multiple emulsions and a comparison with the release of a single agent

In vitro release of salol and benzoic acid from internal droplets of O1/W/O2 double emulsions was investigated in a stirred tank. The molecular structures of both ingredients are presented in Fig. 1. Active agents were released from internal droplets (O1) to the external phase (O2) of multiple emulsions. The release kinetics of both ingredients in the form of the cumulative mass fraction are presented in Figs. 3–5. Salol was released faster from emulsions formed at a lower rotational frequency of the inner cylinder in the CTF apparatus compared to the emulsions obtained at higher rotational frequency. Emulsions formed at a lower rotational frequency of the cylinder were characterized by smaller mean Sauter diameters and greater polydispersity of internal droplets compared to the emulsions obtained at higher rotational frequency. Benzoic acid, likewise, as salol was released faster from the emulsions formed at a lower rotation frequency of the cylinder compared to the emulsion formed at higher frequencies.

Multiple emulsion stability studies confirmed the established diffusional release mechanism. Internal phase (oil phase- O1) droplets were stable within one month in the majority of the tested sets. In all five examined sets of multiple emulsions, membrane phase (water phase) drops were stable in time when both active agents were released which proved the established mass transport mechanism. Active agents were released through the membrane phase, and it was the phase that stability limited the time of the diffusional release. Moreover, simultaneous release of two different active ingredients showed the mutual influence of the presence of both components on the release rates and also on the shape of the profiles. In five examined sets of multiple emulsions, benzoic acid was released faster than salol, as a one-step process. Salol was released as a two-step process. In the first step of salol release, both active ingredients were released simultaneously. The second step of salol release started just after the whole benzoic acid was released.
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Fig. 3. The experimental release profiles of salol and benzoic acid from ME-2A and ME-3A sets of double emulsions formed under the rotational frequency of the inner cylinder in the CTF apparatus 1622 rpm (points represent mean value ± SD, error bars not visible, mean errors are the same size, or smaller, than the symbol for a given measurement).

Fig. 4. The experimental release profiles of salol and benzoic acid from ME-2B and ME-3B sets of double emulsions formed under the rotational frequency of the inner cylinder in the CTF apparatus 1802 rpm (points represent mean value ± SD, error bars not visible, mean errors are the same size, or smaller, than the symbol for a given measurement).

Fig. 5. The release profiles of benzoic acid or salol from multiple emulsions with two co-encapsulated ingredients (points represent mean value ± SD, error bars not visible, mean errors are the same size, or smaller, than the symbol for a given measurement).

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An example of release profiles of two encapsulated active agents is presented in Fig. 6 for the best double emulsion characteristic (set ME-3B) and high stability of both dispersed phases (one month). Nevertheless, it is important to admit that in set ME-3A the salol was released quickly, and the two-step process was not that evident as for other double emulsions because the first step of salol release lasted only half an hour (Fig. 5).

The reasons for the two-step salol release profile could be a difference in structures (Fig. 1) and molecular weight of encapsulated active agents. The molecular mass of salol (214.22 g/mol – PubChem CID 8361) is almost double that of acid (122.12 g/mol – PubChem CID 243). As the benzoic acid is a much smaller molecule than salol, this could ensure its faster release from multiple emulsions (Figs. 3–6). Initially (step I, Fig. 6), the rapid transport of acid molecules through the membrane phase probably impeded the release of larger salol molecules from the internal droplets. Additionally, this effect may be due to the significant difference in solubility of salol and benzoic acid in the aqueous phase (for salol: 0.15 mg/cm$^3$, for benzoic acid: 3400 mg/dm$^3$, at 25 $^\circ$C – PubChem CID 8361; PubChem CID 243). Furthermore, simultaneous salol and benzoic acid release may be related to the initial release of salol present after the encapsulation process next to the interface: inner droplets/membrane phase drops of double emulsions. When the encapsulated benzoic acid is released completely within the first step (step I) of the process, its molecules do not limit the diffusion of salol through the membrane phase, observed as the following step (step II), Fig. 6. In order to compare the release profiles of salol, as the only substance encapsulated in multiple emulsions (ME), and in the presence of benzoic acid (ME-2B and ME-3B), the results of earlier studies of the authors with salol as one encapsulated ingredient were used (Dluska and Markowska-Radomska, 2010; Markowska-Radomska and Dluska, 2012), (Fig. 7). The compared emulsion systems were prepared under similar conditions that ensured obtaining emulsions with similar internal structures. Former studies of double emulsions (O1/W/O2) containing salol as one encapsulated active agent has shown one-step release profiles. An example of a release profile for salol as one ingredient and co-encapsulated ingredient from double emulsion is presented in Fig. 7.

The comparison of the release profiles showed that the presence of the second ingredient (benzoic acid) significantly changed the release kinetics. If salol was released as the only active agent in emulsions, the process kinetics was one-step, while the system with an additional ingredient (benzoic acid) exhibited a two-step course of the release kinetics. The addition of benzoic acid as a second active compound of the
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Fig. 7. Comparison of salol release profiles of salol from ME-2B and ME-3B emulsions (systems with two encapsulated active agents) and ME (system with one encapsulated active agent: salol – data from previous work of the authors (Dluska and Markowska-Radomska, 2010; Markowska-Radomska and Dluska, 2012): $D_{32} = 66.6\ \mu m$, $d_{32} = 32.7\ \mu m$, $\phi = 83.00\%$, the concentration of salol = 10%wt.). Points represent mean value ± SD, error bars not visible, mean errors are the same size, or smaller, than the symbol for a given measurement.

The encapsulation process in the internal phase of double O1/W/O2 emulsion also reduced the time necessary to the total release of salol.

4. CONCLUSIONS

This paper presents the results of an antiseptic and an agent preventing growth of microorganisms co-encapsulated and released from double O1/W/O2 emulsions for topical skin application. Multiple emulsions due to their composition and structures can be used for dermatological purposes, especially in products that help maintain or improve skin conditions. The results obtained allowed us to confirm the assumed diffusivemechanismofthereleaseprocess. The diffusive release mechanism was confirmed by microscopic observations of the state of droplets during the release process and by the lack of significant changes in the characteristics of the emulsion. Under the tested shear stress conditions during the release process, the droplets did not break down or deform. The release of salol in the tested systems with benzoic acid was found to occur in two steps, while the release studies of salol, as a single component encapsulated in the inner emulsion droplets, showed a one-step release profile. The studies showed that benzoic acid was released faster than salol from the emulsion droplets. Based on the comparison of the structures of salol and benzoic acid. It can be concluded that the increase in the release rates resulted from the smaller molecular size and lower molecular weight of the acid compared to that of salol. Also, the higher solubility of benzoic acid in water resulted in a faster release of this agent. The studies carried out for emulsions with two encapsulated agents (salol and benzoic acid) in droplets of the internal phase suggest that the process of salol release can be modulated by the addition of another suitable substance to obtain the desired release time or rates. These systems may play an important role in the design of dosage forms that deliver the drug at the right time and in the right amount, which provide more benefits than conventional dosages. They allow the drug to be released rapidly or slowly (as needed) and completely in a pulsatile way after a required delay time. They may be designed for drug delivery according to the circadian rhythms of the body (e.g., the release of one component during the day, and another at night, or when nocturnal dosing is required). Active agents/drug formulations such as multiple emulsions provide a modified release and potentially could be useful as antiseptic agent delivery systems and for selecting the dose of a drug for
a patient, including oncological treatments. Moreover, such a formulation, with encapsulated antiseptic agents in the internal drops, may be useful for hand hygiene purposes, including wounded skin or for preparation before any medical procedure.

SYMBOLS

\( \phi \) \quad \text{volume fraction of internal phase droplets in the membrane phase drops, \%}

\( D_{10}, d_{10} \) \quad \text{arithmetic mean diameters of drops of membrane and internal phases, \( \mu m \)}

\( D_{32}, d_{32} \) \quad \text{the Sauter mean diameters of drops of membrane and internal phases, \( \mu m \)}

\( D_{43}, d_{43} \) \quad \text{De Brouckere mean diameters of drops of membrane and internal phases, \( \mu m \)}

PDI \quad \text{polydispersity index, –}

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