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Research paper

Active packaging for topical cosmetic/drug products: A hot-melt extruded preservative delivery device

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ABSTRACT

A delivery device intended for the prolonged release of antimicrobial agents, able to enhance the stability profile of liquid/semi-solid cosmetic/pharmaceutical products for topical application, was proposed in the present study. With the aid of a simulation program based on compartment models, the relevant kinetic and formulation parameters were defined using dehydroacetic acid sodium salt (DHA.Na, Prevan®) as the model preservative. Indeed, the overall DHA.Na degradation rate is increased in the presence of formaldehyde releasers that are often employed as co-preservatives. Inert matrices (3 g weight and 18 mm diameter) based on high-density polyethylene (HDPE), possibly consistent with the design of an *active packaging* meant for preservative delivery, were prepared by hot-melt extrusion. Units with satisfactory physical-technological properties could be obtained up to 50% w/w loads of antimicrobial agent. In an attempt to modify the relevant Fickian release profiles by varying the area exposed to the medium, matrix systems coated with an impermeable film except for one base (CMs) or for the inner surface of a central drilled hole (PCMs) were investigated. On the basis of the *n* exponent of power equation and the outcome of linear fitting, PCMs were proven able to yield the zero-order release behaviour needed to ensure constant DHA.Na levels over a predetermined time period, as indicated by the simulation process.

1. Introduction

As far as liquid or semi-solid cosmetic/drug products intended for topical application are concerned, much research effort has been addressed to the identification of new preservatives, which may ensure an effective antimicrobial protection without associated toxicity issues and risk of allergic sensitization [1]. However, the possibility of meeting specific stability-related needs by means of preservative delivery systems could be of high interest. These might indeed yield improved antimicrobial protection through the use of substances with consolidated tolerability profiles and even allow the amount of preservatives to be reduced. The use of packaging systems not only intended for passive protection against humidity, light and oxygen, but also designed to improve the overall quality characteristics of their contents, e.g. to extend shelf-life and enhance safety or sensory properties, is a well-known concept for food products [2–4]. With regard to *active packaging* technologies, the most innovative applications relate to the sustained release of antimicrobial, antioxidant and anti-browning agents over time to replenish the amount consumed and/or target the food surface where spoilage reactions predominantly occur [5–10]. Moreover, it has been suggested that amounts of preservative slowly added can act synergistically with the initially included ones, thus improving the overall antimicrobial protection [11].

Dehydroacetic acid and its derivatives, such as the sodium salt (DHA.Na, Prevan®), are well-known preservatives exhibiting both fungicidal and bactericidal activities. They have found application in the antimicrobial/anti-moulding protection of foods, drug products and cosmetics. In the latter, in particular, they are permitted at specified maximum concentrations (0.6% for the acid) [Directive 86/199/EEC]. Since mixtures of antimicrobials can ensure broader activity profiles than individual agents and allow smaller amounts of each component to be employed, DHA.Na is often combined with formaldehyde (HCHO)-releasers [12–14]. However, due to its high reactivity in the presence of HCHO, an ineffective tricyclic compound is formed leading to a loss in the antimicrobial protection [13]. Accordingly, a matrix-like delivery system was proposed intended to provide effective levels of DHA.Na over time by compensating for the fractions that interacted with *in situ*-generated HCHO [15,16].

On the basis of these premises, in the present work, delivery devices containing antimicrobial agents that could be associated with cosmetic/pharmaceutical packaging (*active packaging*) are

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proposed. The preservative release into liquid/semi-solid formulations should start at the time of the first opening of the product. Preliminary studies for the design of such a device were carried out selecting DHA.Na as the preservative molecule and water as a model release fluid. Based on the kinetic parameters of DHA.Na degradation, in particular, an assessment of the appropriate release behaviour required from a hypothetical delivery system was carried out with the aid of a modelling simulation program (STELLA®). Prolonged-release inert matrices containing DHA.Na, potentially suitable for insertion in tubes/bottles, were prepared by hot-melt extrusion and evaluated for release performance. The influence of the device geometry on the release rate was also investigated.

2. Materials and methods

2.1. Materials

Dehydroacetic acid sodium salt (DHA.Na, Prevan®, Dott. Formenti S.p.A., Milan, I), water solubility at 20 °C 33%, melting temperature around 290 °C; high-density polyethylene (HDPE, Hiplex® Type TR130, Petrohemija, Pančevo, SR); cellulose acetate propionate (CAP 482-20, Eastman-Kodak, Kingsport, UK); FD&C lake red (Eigenmann & Veronelli, Rho (MI), I).

2.2. Methods

2.2.1. Matrix preparation

Binary DHA.Na/HDPE matrices were prepared by hot-melt extrusion using a single-screw extruder (Extrusiograph 19/25D, Brabender GmbH&Co. KG, Duisburg, D) equipped with a rod-shaped die (∅18 mm) under the following processing conditions: screw speed, 15 rpm; temperatures, 190 (barrel zone 1), 200 (barrel zone 2), 205 (barrel zone 3) and 190 °C (die); time, 5 min. Prior to use, DHA.Na powder (size fraction <300 μm) was dried in a ventilated oven (60 °C) for 24 h. Blends consisting of 20, 30 and 50% w/w DHA.Na and 80, 70 or 50% w/w grinded HDPE (size fraction <500 μm) were prepared by mixing in Turbula® (Type T2A-Willy A. Bachofen AG, Muttenz, CH) for 10 min. Extrudates were stored at room temperature for 48 h and subsequently cut into cylindrical matrices (Uncoated Matrices, UMs) with a bench-top saw. UMs were characterized for weight, diameter, thickness and preservative content.

To prepare Coated Matrices (CMs), UMs were coated on the whole surface except for one base by immersion in CAP 482-20 15% acetone solution containing FD&C lake red colourant.

Perforated Coated Matrices (PCMs) were prepared by completely coating UMs with the above-mentioned polymeric solution and then drilling a central hole (diameter 4 mm) in the coated systems (4% weight loss).

Coated systems were stored for 24 h at room temperature (21 ± 2 °C) and relative humidity (55 ± 5%) conditions before the release test.

2.2.2. Release test

In order to evaluate the amount of DHA.Na delivered, each matrix system was placed into a borosilicate glass flask sealed with a frost glass stopper containing 250 ml of distilled water. Flasks were maintained at room temperature (21 ± 2 °C). According to the DHA.Na self-degradation kinetics [15], the release medium was completely replaced every 5 days. Prior to analysis, the flasks were manually agitated upside-down for 2 min, and the DHA.Na concentration was assayed spectrophotometrically at 295 nm (Spectracomp 602, Advanced Products, Milan, I) in the withdrawn fluid. Only in the case of UMs, daily analysis was performed in the first 10 days.

Release profiles are average cumulative curves ($n = 3$); bars in figures represent standard deviation (s.d.).

Data were fitted according to power equation [17]:

$$M_t/M_\infty = Kt^n$$

where M_t/M_∞ is the fraction of active substance released at time t, K is the kinetic constant and n is the diffusional exponent. K and n depend on structural and geometric characteristics of the system. Data were fitted up to $M_t/M_\infty = 0.6$.

2.2.3. SEM analysis

Photomicrographs of UMs before and after 10-day release testing were collected on gold-sputtered samples (sputter time 120 s) with a Stereoscan 200 Scanning Electron Microscope, SEM (Cambridge Instrument Company, Cambridge, UK; voltage 30 kV).

2.2.4. Simulation study

A compartment model was constructed by means of a graphics-based software package (STELLA®, Isee systems, Lebanon, NH, US) for Mac OS environment. The simulation process was carried out on the basis of given inputs connected with effectiveness and degradation kinetics of DHA.Na as well as expected formulation and stability characteristics of the product.

3. Results and discussion

Previous studies carried out on DHA.Na alone and in the presence of increasing amounts of formaldehyde in aqueous solution indicated that a pseudo-first-order degradation kinetics was involved and that the degradation rate constant increased as a function of HCHO concentration [13,15]. These results suggested that the stability of DHA.Na in aqueous solution containing formaldehyde-donor preservatives would be dependent on both its self-degradation and *in situ* reaction with the produced HCHO. Therefore, in order to maintain effective concentrations of preservative, higher DHA.Na loads should be used possibly resulting in sensitization and adverse reactions. Antimicrobial protection may also be ensured by continuously supplying the formulation with preservative so as to compensate for its degraded fractions. Accordingly, inert matrix systems were proposed to control the rate and duration of DHA.Na release.

Based on these premises, the design of such matrices was improved with the aim of achieving predictable zero-order release kinetics on the one hand, and inherent morphological features (shape and dimensions) that may enable association with the primary packaging of topical cosmetic/pharmaceutical products on the other. In order to undertake a rational formulation study, a simulation approach was employed.

The essential steps needed for the simulation process are summarised below:

- *step 1:* to establish the effective level of DHA.Na required to ensure antimicrobial activity during the entire shelf-life of the product;
- *step 2:* to define the degradation rate of DHA.Na in the specific formulation;
- *step 3:* to assess the rate of DHA.Na release from the delivery system in order to comply with requirements of step 1.

A compartment model was constructed using STELLA®, a simulation software that is widely applied in the pharmaceutical field and particularly in pharmacokinetic studies [18–21]. The model involves DHA.Na release from an external source, e.g. the delivery system, into the formulation from which the antimicrobial agent is removed by degradation according to a first-order process

(Fig. 1). In order to maintain a steady-state concentration of DHA.-Na in the formulation, a zero-order release kinetics was imposed.

Before running a simulation process based on this model, a number of operative parameters needed to be defined, such as (i) effective DHA.Na level, i.e. the preservative concentration to be maintained in the formulation to ensure protection during the whole shelf-life and (ii) DHA.Na degradation rate. An example of operative simulation is reported in Fig. 2. Values typical of commercial cosmetic products were selected as inputs, except for DHA.Na degradation rate constant that was derived from the above-mentioned experimental data relevant to the preservative degradation kinetics [15]. The initial DHA.Na concentration was set at approximately 70% of the maximum level permitted [Directive 86/199/EEC]. The obtained simulation profiles show the concentration of DHA.Na in the formulation when no external source of preservative is present (A) and when the delivery system is operating (C), as well as DHA.Na release here expressed as the amount remaining in the device (B).

The simulation process indicated that in order to keep consistent DHA.Na levels >1 mg/ml over a one-year period, a delivery system should be designed to constantly release 2.5 mg/day and contain 900 mg of the antimicrobial agent. Initial amounts much higher than 900 mg would be required to maintain effective DHA.-Na concentrations throughout the same time interval with no external source, thus largely exceeding the admitted preservative level. Therefore, a further important advantage related to the use of a delivery system intended for prolonged DHA.Na release would consist in an improved product safety/tolerability due to the lower amount of preservative needed.

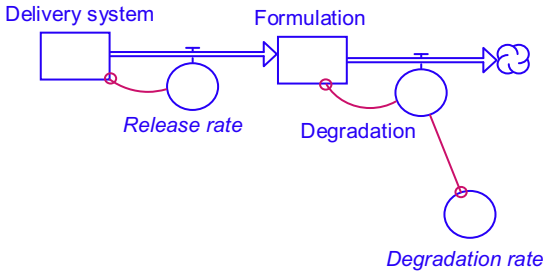

Fig. 1. STELLA® release compartment model.

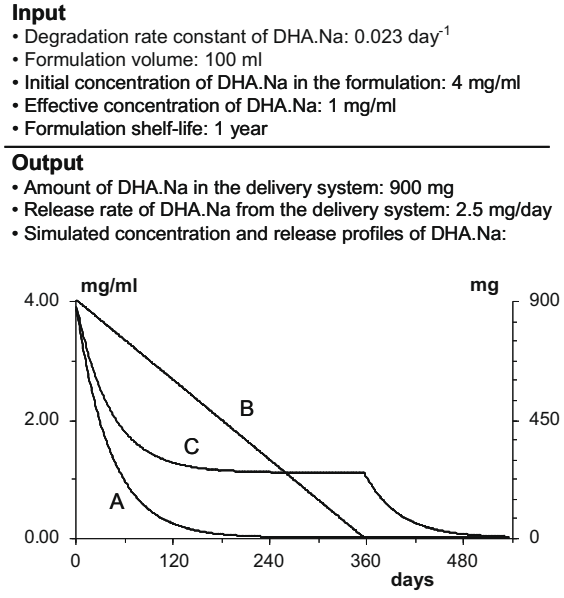

Fig. 2. Inputs and outputs of the simulation process. (A) Concentration profile of DHA.Na in the formulation according to its degradation kinetics when no DHA.Na external source is present; (B) amount of DHA.Na remaining in the delivery device; (C) concentration profile of DHA.Na in the formulation when the delivery system is operating.

Along with the simulation attempts, formulation studies were also undertaken in order to achieve matrix delivery systems not only able to release the proper amount of antimicrobial agent at a programmed rate for a predetermined time period, but also suitable for being matched with the packaging or proposed as inherent relevant constituents. In this respect, high-density polyethylene (HDPE) was selected as the matrix-forming agent, since it is widely used in the pharmaceutical, healthcare and cosmetic industry for the manufacturing of bottles, cans, caps and closures. Pharmacopoeial grades of HDPE, in particular, are available for the production of extruded containers. Based on the simulation findings, cylindrical DHA.Na/HDPE matrices (Uncoated Matrices, UMs) with approximately 20 mm diameter were accordingly prepared by hot-melt extrusion. In order to preliminarily evaluate the possibility of achieving different release rates, increasing preservative/polymer% ratios were considered. Therefore, units with analogous weight and size containing 20, 30 and 50% w/w (600, 900 and 1500 mg) of antimicrobial agent were prepared.

All units exhibited good physical-technological properties (Table 1). Content uniformity was also obtained in the case of matrices with the highest preservative load, i.e. in the most critical process condition. SEM photomicrographs showing the surface of such extruded matrices prior to immersion in distilled water and following 10 days of release test are reported in Fig. 3.

As 20–50 mm diameter plastic tubes are generally available as packaging for cosmetic or drug products, the insertion of preservative matrices in the bottom end of a container was initially hypothesized. In a further configuration development (*active packaging*), packages with a pre-formed *functionalized* portion could be devised. In any case, the release area of the preservative-containing system would most likely be restrained. UMs were thus provided with a water-impermeable film on the whole surface except for one base to give Coated Matrices (CMs), from which unidirectional release could be achieved [22,23].

Moreover, based on the well-known relationship between area of matrix/solvent interaction and rate of release, a design strategy aimed at modifying the typical Fickian (non-zero-order) inert matrix kinetics was approached [24]. For this purpose, Perforated Coated Matrices (PCMs) were prepared by drilling a central hole into matrices that were completely coated with the impermeable film [25,26]. As solvent penetration was only allowed through the perforation, a progressive increase in the matrix/release medium interaction area was expected.

The above-described matrices and relevant release profiles are shown in Figs. 4 and 5, respectively.

The release profiles of DHA.Na from UMs showed a typical matrix pattern with a starting burst and a subsequent progressive decrease in the amount of preservative delivered over time. A reduced release rate was observed in CM profiles because of the

Table 1
Physical-technological characteristics of UMs (Uncoated Matrices).

Formulation (DHA.Na:HDPE, % w/w)	Diameter (mm ± s.d.[a])	Thickness (mm ± s.d.[a])	Weight (g ± s.d.[a])	DHA.Na content (g ± s.d.[a])
20:80	20.66 ± 0.32	8.03 ± 0.16	3.12 ± 0.11	0.62 ± 0.02
30:70	20.18 ± 0.41	8.51 ± 0.13	3.01 ± 0.12	0.89 ± 0.03
50:50	19.79 ± 0.44	9.26 ± 0.11	2.93 ± 0.06	1.47 ± 0.05

[a] Standard deviation.

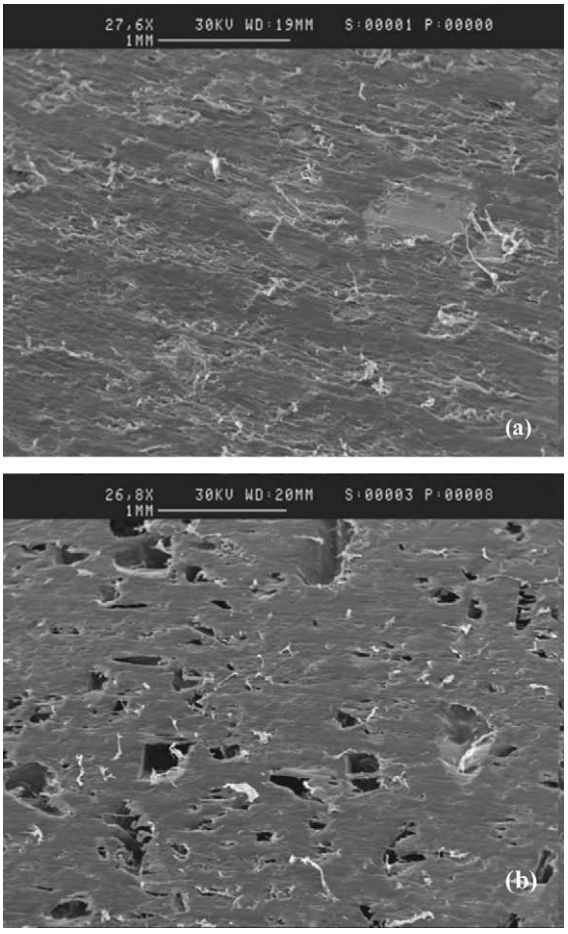

Fig. 3. SEM photomicrographs of the surface of extruded matrices (50% w/w DHA.Na) before (a) and after 10-day release testing (b).

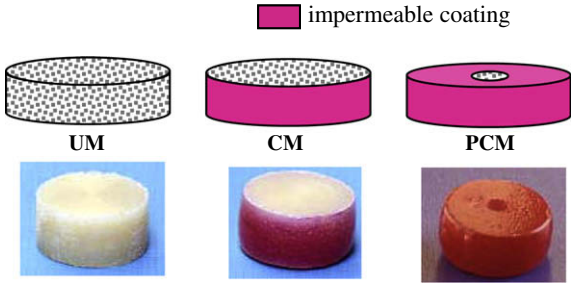

Fig. 4. Sketches and photographs of UM (Uncoated Matrix), CM (Coated Matrix) and PCM (Perforated Coated Matrix) systems.

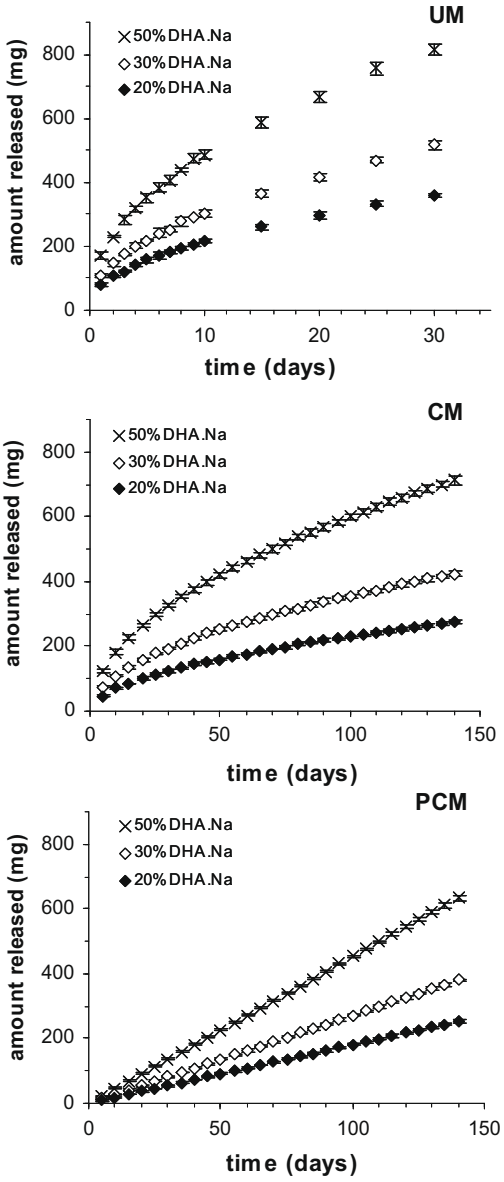

Fig. 5. Release profiles of DHA.Na from UM (Uncoated Matrix), CM (Coated Matrix) and PCM (Perforated Coated Matrix) systems (250 ml distilled water, $n = 3$, bars indicate s.d.).

limited surface area exposed to the medium, whereas a nearly constant release rate was observed in the case of PCMs. As initially assumed, higher release rates were always achieved by increasing the preservative/polymer ratio.

It is well-known that the liberation of soluble components from heterogeneous inert matrices takes place by diffusion through a medium-filled pore network. During the release process, two different zones can be defined inside the matrix, the one in contact with the medium being subject to gradual depletion. The solvent penetration front defines the *effective* release area, i.e. an interface where the medium comes into contact with active ingredient particles so that the dissolution process can start. In UMs, a progressive decrease in this area and lengthening of the diffusion path occur, both resulting in a decreased rate of delivery. As far as CMs are concerned, solvent penetration and drug release can only take place through the uncoated base. While the matrix is in contact with the medium, the penetration front moves away from the exposed surface, thus increasing the length of the diffusion path. However, the *effective* release area can be regarded as constant. Consequently, the decrease in the delivery rate is lower when compared with UMs. Finally, the penetration of solvent into PCMs proceeds from the central hole in the radial direction, thereby bringing about a progressive increase in the area that may counterbalance the diffusion path lengthening. When this condition is accomplished, a constant release rate can thus be achieved [25]. The changes that take place in the *effective* release area of the different matrices when exposed to the solvent are depicted in Fig. 6.

In order to assess the impact of the design modifications described, matrix release data were fitted to the well-known power equation (Table 2) [17].

According to Colombo and co-workers [27], who previously applied the above-mentioned equation to comparatively evaluate the

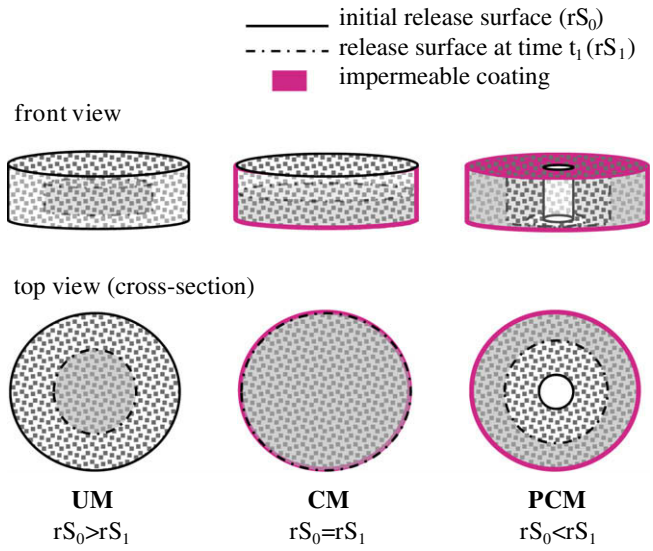

Fig. 6. Front and top views of matrix systems at time t_1 during the release test (UM: Uncoated Matrix; CM: Coated Matrix; PCM: Perforated Coated Matrix). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Power equation fitting parameters of DHA.Na release data.

System	DHA.Na content (% w/w)	Exponent *n*	*n* LoConf[a]	*n* UpConf[b]	r^{2c}
UM	20	0.45	0.44	0.46	0.994
	30	0.46	0.45	0.47	0.994
	50	0.46	0.45	0.47	0.995
CM	20	0.52	0.52	0.53	0.996
	30	0.52	0.51	0.52	0.998
	50	0.52	0.51	0.53	0.998
PCM	20	0.99	0.98	1.00	0.998
	30	0.99	0.98	1.00	0.999
	50	0.99	0.98	0.99	1.000

[a] 95% Lower confidence limit of exponent *n*.
[b] 95% Upper confidence limit of exponent *n*.
[c] Regression correlation coefficient.

release mechanism of inert *vs* hydrophilic matrices, diffusion-controlled delivery was confirmed for UMs and CMs on the basis of the *n* exponent values calculated. Indeed, $n \cong 0.45$ and $n \cong 0.5$ were obtained, consistent with the device geometrical characteristics, for cylindrical matrices (UMs) and systems with a planar surface exposed to the medium (CMs), respectively. On the other hand, the higher *n* exponents ($\cong 1$) of PCMs could indicate, in a merely descriptive way, that a shift toward zero-order kinetics was obtained. To confirm these findings, release data of these systems were subjected to linear fitting (Table 3).

Table 3
Linear regression parameters of release data from PCMs (Perforated Coated Matrices).

Parameter	DHA.Na amount (% w/w)		
	20	30	50
Slope	1.81	2.71	4.52
LoConf [a]	1.79	2.69	4.50
UpConf [b]	1.82	2.72	4.53
Intercept	0.74	0.84	1.39
LoConf [a]	−0.28	−0.47	−0.12
UpConf [b]	1.75	2.72	2.90
r^{2c}	0.999	0.999	1.000

[a] 95% Lower confidence limit.
[b] 95% Upper confidence limit.
[c] Regression correlation coefficient.

The fitting was satisfactory, and release rates turned out to be in the 1.8–4.5 mg/day range, which was consistent with the output of the simulation process.

The obtained results indicated that by modifying the design characteristics of matrix devices, differing preservative release kinetics and *functionalized* packaging configurations could be achieved.

4. Conclusions

The present study deals with the problem of ensuring an effective antimicrobial protection for topical cosmetic/drug products. In this respect, the design of an *active packaging* able to supply liquid or semi-solid formulations with the proper amount of preservatives over time was hypothesized. In particular, DHA.Na was selected as a model antimicrobial agent because, in addition to its self-degradation, it was reported to undergo a progressive decay when combined with formaldehyde-donor preservatives.

Relying on experimentally assessed kinetic data of DHA.Na degradation, the main formulation parameters of a potential delivery device, i.e. the amount and release rate of the antimicrobial agent, were identified by means of a simulation approach based on compartment models. Inert matrices with differing design features were subsequently prepared by hot-melt extrusion employing HDPE, a polymeric material that is commonly used for cosmetic/pharmaceutical packaging. Perforated cylindrical systems coated with an impermeable film except for the surface delimiting the inner hole were shown to yield the required linear release patterns, at least in the model fluid considered (distilled water). Indeed, the behaviour of such devices in different release media (viscous solutions, emulsions, semi-solid formulations) needs to be in-depth investigated in order to take account of further variables, such as the possible impact of preservative diffusion within the final product.

The overall results highlight the possibility of obtaining, by means of a scalable continuous manufacturing technique, systems able to release antimicrobial agents at programmed rates, which might be consistent with the packaging of cosmetic/drug products.

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