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Stability and applicability of retinyl palmitate loaded beeswax microcapsules for cosmetic use

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Abstract

In our previous study, retinyl palmitate was successfully encapsulated by melt dispersion using waxes as shell materials. Herein, the objective of the present research is to evaluate the shelf life and kinetic release of the developed microcapsules. The study was conducted by measuring actual loading capacity over a period of time using spectroscopic analysis. The transfer percentage of particles from nonwoven facial wipes to skin-like surfaces was also investigated by simulating the rubbing mechanism with a robotic transfer replicator. Although particles stored as powder form under room temperature showed only eight days of shelf-life, particles stored as a dispersion in a refrigerator maintained 60% of the theoretical loading capacity after one month. The kinetic release profile of the particles in ethanol with shaking at 100 rpm and 37± 2ºC showed an initial burst in the first half an hour, followed by a sustained release. It also showed that 98% of the retinyl palmitate content released within 4 hours. Particles incorporated into wet nonwoven wipes gave approximately 22% transfer to skin-like fabric. Thus, the study shows potentials of delivering skincare properties by means of retinyl palmitate capsule loaded textile substrates.

Keywords: Microencapsulation; retinyl palmitate, anti-aging, stability, spectroscopy, chemical analysis.

Introduction

In cosmetic science and technology, retinoids are widely recognized to address skin concerns, such as acne, rosacea, pigmentation, and symptoms of photoaging [1]. Retinoids are chemical compounds of vitamin A, which include retinoic acid, retinal, retinol, and retinol derivatives. Retinoic acid has been well researched and found to be effective as a topical treatment for photoaging, hyperpigmentation, wrinkles, and dry skin [2-5]. However, many patients suffer from retinoid dermatitis as a side effect of the aggressive reaction of retinoic acid [6]. Therefore, researchers have been studying retinol and its derivatives for cosmetic applications to impart the benefits by minimizing the irritation on the skin [7-10]. After being topically absorbed by the skin, retinol, retinal, and their derivatives need to enzymatically convert into a biologically active form, i.e., retinoic acid through oxidative processes [11]. The chemical structures of the retinoids and their mechanism of skin treatment is discussed in our previous work [12].

Many studies revealed that topically applied retinoids, including retinyl palmitate (a lipophilic, ester derivative of retinol), are effective in skin penetration, percutaneous absorption, metabolization to retinol and retinoic acid, and skin treatment. [13-20]. However, instability has been a challenge to incorporate retinoids into cosmetics due to oxidation of retinol over time and its sensitivity to heat and light [21, 22]. Microencapsulation can solve this problem by protecting active ingredients from reactive compounds in formulations as well as releasing them when applied on to the skin [23]. In the perspective of cosmetic formulations, retinoids have been reported to be successfully encapsulated. Torrado et al. demonstrated encapsulation of retinol palmitate in albumin by emulsion method, where coagulation of the the emulsion followed by decantation facilitated the isolation of albumin microspheres [24]. Jenning et al. encapsulated vitamin A into glyceryl behenate through dispersion of hot lipid phase and high pressure homogenization [25]. Retinol-chitosan microparticles were prepared by Kim et al., using ultrasonication and

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evaporation of solvent [26]. Gangurde and his group reported microencapsulation of vitamin A palmitate in maltodextrin /modified starches using spray drying method [27]. We have explored the potential of the melt dispersion method to successfully encapsulate retinyl palmitate [12]. The employed melt dispersion method is an inexpensive, environment-friendly method with minimum use of synthetic chemicals.

In order to assess the quality of topical products containing active substances, tests include content uniformity analysis, pH measurement, the content of water and preservatives, particle size analysis, assays, etc. [28]. Gangurde and Amin [27] described the separation of oil/water phases, change in color, inconsistency of formulation, and development of unpleasant odor as some indications of the instability for vitamin A palmitate microcapsules. In this study, we evaluated the visual change in color and retention of retinyl palmitate content to understand the stability as well as the shelf life of prepared microcapsules.

In vitro kinetic release studies are performed to understand the release rate of active ingredients in the body and also to understand the storage stability. The mechanism of the controlled release of active ingredients can be broadly categorized into physical and chemical mechanisms. According to Acharya and Park [29], the physical mechanisms may involve diffusion of the drug through the polymer matrix, degradation or dissolution of the polymer layer, osmotic pressure, or use of ion exchange for ionized drugs. On the contrary, the chemical mechanism involves the alteration of active molecules [30]. In the case of waxy materials as matrix components, the most significant release mechanisms of active ingredients are the diffusion of the active core through the matrix and erosion of wax matrix through ester hydrolysis reaction [31].

Topically applied active ingredients are often incorporated into a carrier such as creams, gels, or textile substrates to ensure targeted trans-dermal delivery. Microcapsules can be

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incorporated into textile substrate by means of coating, impregnation or immersion, spraying or printing [32]. Several studies have investigated the application of microencapsulation in cosmetic textiles. Yamato et al. formulated treatment liquids containing microcapsules of skin-care substances and binding agents and incorporated them into textile structure through spraying [33]. Wang and Chen prepared aroma-therapeutic textile with fragrance-loaded cyclodextrin inclusion compound by conventional pad-thermo fixing method [34]. Koenig formulated a cleansing composition with microencapsulated delivery vehicle comprised of active agents that can be introduced into wet wipes by various means [35]. Cheng et al. developed vitamin C-loaded gelatin microcapsules using emulsion hardening process that can be grafted into textiles to impart skin-care benefits [36]. Alonso reported the preparation of polyamide cosmetotextile comprising of gallic acid (GA)-loaded poly-ε- caprolactone (PCL) microspheres to impart antioxidant effect to skin [37]. Fiedler et al. incorporated aloe vera-cornstarch microcapsules obtained through coacervation into cotton nonwoven fabric, where impregnation mechanism was applied by using butane tetracarboxylic acid (BTCA) as a binding agent [38].

Textile-based substrates, as delivery vehicles, have their benefits due to flexibility and ease of application [30]. The open, permeable structure, as well as large surface area, make the textile structure ideal support for topical drug delivery applications [39]. Therefore, we aim to explore nonwoven facial wipe as a mean to incorporate microcapsules containing retinoids and evaluate the transfer of microparticles from the substrate to skin.

In our previous work, we successfully encapsulated retinyl palmitate using waxes as shell material [12]. Natural waxes such as beeswax are skin-friendl,y and popular as cosmetic additives. Beeswax has anti-inflammatory and antimicrobial properties, suitable for topical treatment [40, 41]. Besides, beeswax is also efficient to improve the barrier function of the skin [42].

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The overall objective of the present study was to evaluate the shelf life and kinetic release of the developed microparticles by measuring the loaded content of retinyl palmitate over time and also to investigate the simulated transfer of microparticles from the wet nonwoven substrate to skin-like fabric by using a robotic transfer replicator.

Materials and methods

Materials

Refined, white beeswax pearls and retinyl palmitate (vitamin A) of 1.7 M.I.U./g. were purchased from Bulk Apothecary (Aurora, OH) and Fisher Scientific USA (Pittsburg, PA), respectively. Ethanol was obtained from Decon Labs, Inc. (King of Prussia, PA). Compression fabric (warp knit: 77% nylon and 23% spandex) was obtained from the Marena Group (Lawrenceville, GA). Pampers aqua pure™ nonwoven wipes were also used as a carrier to transfer microparticles from the substrate to skin.

Microencapsulation of retinyl palmitate and effect of process variables

We microencapsulated retinyl palmitate (RP) by melt dispersion technique and investigated the effect of four process variables on the produced microcapsules, such as different theoretical loading capacity (10%, 15%, 25%), types of wax (beeswax, carnauba wax, paraffin wax), emulsifier concentrations (0%, 1%, 2%) and stirring speeds (180, 230, 280 rpm) in our previous study [12]. The statistical analysis showed that theoretical loading capacity and surfactant (%) were the most significant factors and we were able to determine that the highest theoretical loading (25%) and highest surfactant (2%) selected in that study can provide us high actual loading with the small size of the particles. There was no significant difference found among the effects of type of wax on loading capacity, encapsulation efficiency, antioxidant activity, or mean size of particles. Hence we decided to conduct further study selecting beeswax as the shell material

because of its natural skin-care benefits as well as operational convenience due to low melting point (65ºC). We selected 280 rpm stirring speed to facilitate dispersion of the oil-in-water emulsion and formation of small size particles.

Thermal characterization by Differential Scanning Calorimetry (DSC)

Thermal analysis of the beeswax, retinyl palmitate (RP), and RP-loaded beeswax microcapsules was carried out by using Mettler Toledo DSC821e (Schwerzenbach, Switzerland) instrument, where a standard empty aluminium pan was used as the reference. The weight of the samples was within 2-9 milligrams, and the samples were scanned from 25ºC to 100ºC under N_2 atmosphere with a heating rate of 10ºC/min.

Shelf life study

After preparing the microcapsules with 25% theoretical loading, we looked into the shelf life of microcapsules by measuring the actual loading percentage, i.e., the content of retinyl palmitate in a fixed amount of capsules over a period of time, both in powder and dispersion forms. We evaluated the shelf life of the beeswax microcapsules (approximately 71% encapsulation efficiency) in powder form, where they were filtered and dried before storing in an enclosed petri dish under room temperature; and also in dispersion form (approximately 75% encapsulation efficiency), where the particles were kept as dispersed within the emulsion during preparation, stored inside dark vials in refrigerator and a portion was filtered on each day of measurement (Day 1, Day 4, Day 8, Day 15, and Day 31).

An extraction from 0.1 g of microcapsules was performed, by heating the capsule in 20 ml of ethanol solution to release the vitamin content and then filtering the wax residue. The concentration of supernatant aliquots was measured at 327 nm by an Shimadzu UV 2401PC spectrophotometer

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(Kyoto, Japan). The amount of retinyl palmitate was determined from a standard curve of known concentrations.

Kinetic Release study

We conducted an *in vitro* kinetic release study similar to prior literature [27, 43], with some modification based on particle content, solvent type, and machine parameters. The retinyl palmitate release profile from 3g of suspended particles (approximately 77% encapsulation efficiency) was examined in 600 ml of pure ethanol. The study was performed in a New Brunswick C24 incubator shaker with a speed of 100 rpm and temperature set at 37± 2 ºC. Supernatant aliquots of 2 ml were withdrawn and replaced by the fresh medium at appropriate time intervals (1 min, 5 min, 15 min, 30 min, 1hour, 2hour, 4hour). The supernatants containing dissolved retinyl palmitate were diluted and analyzed by UV-vis spectroscopy at 327 nm. The results were compared with a standard to calculate the vitamin A concentration and to evaluate the release ratio.

Simulated transfer study from the textile substrate to skin

We used a robotic transfer replicator (Fig. 1) to simulate the transfer of microparticles from a nonwoven wipe to the skin and evaluate the transfer percentage, by means of a similar method as described by Yu et al. [44]. 1 g of microparticles was spread as evenly as possible by a spatula over a commercial nonwoven wipe containing 99% water that acted as a donor surface with a diameter of 133 mm. The receptor material was a compression fabric, i.e., a warp knit with a composition of 77% nylon/ 23% spandex (fabric weight 276 gms/cm^2. This fabric was chosen because the study by Yu et al. [44] regarding transfer of particulates from carpet surface to human skin-like receptors revealed that this fabric replicated the human skin, particularly finger pads best as a receptor material. The receptor fabric was attached to an aluminum nose piece with the help of O-ring made of rubber. After the activation of the replicator, the nose piece descended the

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receptor fabric onto the donor surface and rubbed the receptor against the donor by executing a certain number of motions (imitating an hourglass pattern) under a constant pressure maintained by the programmed hydraulic system. After performing this rub cycle, the nose piece was raised and delivered onto a glass jar containing 20 ml of ethanol. The fabric was released into ethanol and shaken vigorously, followed by sonication for 2 hours so that all the particle content is released into ethanol. Then aliquots were removed for assay in an ultraviolet-visible spectrophotometer to measure the content of retinyl palmitate. Finally, the amount of transfer of retinyl palmitate was calculated in percentage.

Statistical Analysis

All the measurements for shelf life study were performed in triplicates, whereas the measurements of kinetic release study and simulated transfer study were performed in duplicates. The results have been reported as the mean values and their corresponding standard deviations.

Result and discussion

Thermal Analysis

Fig. 2 shows differential scanning calorimetry (DSC) scans of beeswax, retinyl palmitate, and beeswax microcapsules with 25% theoretical loading capacity. In the thermogram of retinyl palmitate, a sharp endothermic peak is observed at 34.33 °C, which corresponds to its melting point. However, it is observed that the microcapsules show no endotherms corresponding to the melting point of retinyl palmitate. This implies that retinyl palmitate dissolved within the matrix of beeswax when the temperature reached its melting point [45]. This observation was consistent with the result found by Milanovic et al. [46], where encapsulated ethyl vanillin dissolved in the carnauba wax matrix. Untreated beeswax and RP-loaded beeswax microcapsules show their

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melting peaks at 65.67 °C and 63°C, respectively. The slight decrease in the melting point of the particle should be due to the mixing of RP and wax because of plasticization. A second peak is observed for microcapsules at higher temperature (slightly higher than melting temperature), which could be because of fraction of large crystallites formed after encapsulation process that showed higher melting.

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Shelf Life

Fig. 3 shows the shelf life study of the beeswax microcapsules in (a) powder form stored under room temperature (b) dispersion form stored in a refrigerator. When the particles were evaluated in powder form under room temperature, the microcapsules lost their active content within 8 days (Fig. 3a) . This phenomenon can be attributed to the diffusion of retinyl palmitate through the wax shell. The high compatibility between lipophilic, low molecular weight active ingredients with wax is the major cause of diffusion [47]. Diffusion can be accelerated in small-sized particles due to the availability of larger contact areas as well as due to pores existing in the shell matrix [48].

Djordjević et al. [31] described the internal structure of particles produced by melt dispersion with the wax shell to be non-homogeneous with matrix or hollow-shell morphology. Therefore in the prepared microcapsules, retinyl palmitate is distributed within the wax shell matrix. With the course of time, the core content comes up to the surface and diffuse through the shell. From Fig. 4a, the gradual change in the color of beeswax microcapsules supports the phenomenon of diffusion as a pluasible explanation. The particles stored as powder form appear to be bright yellow after the RP diffuses to the surface, and they turn white (beeswax) when almost all of the core content leaches out.

On the other hand, when the RP-beeswax particles were stored in the dispersed aqueous emulsion in a refrigerator, they retained the core material and showed no significant decrease in RP content until the 15th day (Fig. 3b). The variability in size distribution of different batches of filtered particles may account for the slight increase observed in actual loading capacity (Fig. 3b). After 30 days, a decrease in loading was observed, which can be explained by ester hydrolysis of the beeswax while stored in aqueous emulsion resulting in the release of the content [49]. RP-

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beeswax particles stored in the dispersed aqueous emulsion in the refrigerator do not show a significant visual difference in color when filtered. (Fig. 4b).

Kinetic Release study

The release profile (Fig. 5) of retinyl palmitate-beeswax microcapsule showed an initial burst followed by a slower release of the vitamin entrapped inside the beeswax matrix. Due to the initial burst effect, 7% of the retinyl palmitate released at the first minute, leading to around 55% release in the first half an hour. After the initial rapid release, the release profile showed a sustained release over time. Within 4 hours, approximately 98% of retinyl palmitate was released. A similar pattern of release was found by Kheradmandnia et al. [49] from ketoprofen-loaded solid lipid nanoparticles incorporated in the matrix of beeswax-carnauba wax mixture. Zigoneanu et al. [50] described the phenomenon of such initial burst as the result of the cumulative effect of diffusion of the core through the matrix, penetration of dissolution medium into the particle, and degradation of the shell matrix. As retinyl palmitate is soluble in ethanol, this explanation is agreeable to our result. Permeation of ethanol through the pores of the shell matrix and simultaneous diffusion of retinyl palmitate through the matrix facilitated the fast dissolution of the vitamin into ethanol. Duclairoir et al. has reported similar release profile for α-Tocopherol from wheat gliadin nanoparticles, where mathematical models were demonstrated for the bistep release, i.e. the burst effect and the slower diffusion process [51]. While the initial burst could not be described by their model, the time-dependent slow release showed a good fit (R^2 =.90) for the model below:

$$\frac{M_t}{M_0} = 6\sqrt{\frac{\tau}{\pi}} - 3\tau \text{ , where , } \tau = \frac{Dt}{R^2}$$

Here, M_0 is the amount of active content incorporated, M_t is the amount of release core at time t, D is the diffusion coefficient, and R is the radius of the particle. Thus the sustained release was

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related to the diffusivity of the active core inside the matrix system, the surface area of the particle and the loaded content.

From this result, we can understand that alcohol-based cosmetic formulations will not be stable over time as the core content would be released in the carrier substrate during the storage period, making RP susceptible to oxidation and degradation. On the contrary, as we already observed in the shelf life study, an aqueous medium prevents the active content from releasing from the capsule because of having no affinity to the lipophilic content. As a result, a water-based formulation would be suitable to contain the particles for cosmetic applications.

Simulated transfer study from the textile substrate to skin

From the transfer study, we found that 21.7± 0.02 % of retinyl palmitate was transferred to the receptor material from the donor surface of wet nonwoven wipe after the pre-programmed rubbing cycle. The percentage falls within the range reported by Yu et al in their study of transfer of particulates from carpet surfaces to human skin. Although this amount may vary depending on encapsulation efficiency, method of particle incorporation, and the amount of particle incorporated, this study demonstrates the potential of using such microparticles into facial wipes to impart skin-care properties. H. Knaggs, in his skin-aging handbook, mentioned that 0.05-0.1% tretinoin (retinoic acid) was effective to reduce signs of aging in Asians [52]. Oliveira et al. demonstrated in their study that topical application 1% RP has promising results for the treatment of skin aging [53]. According to Gangurde et al., the recommended concentration for topical semi-solid formulation of vitamin A palmitate is 0.05% - 0.3% [27]. Thus, considering the approved dosage of retinoids, absorption and conversion rate of retinyl palmitate to retinoic acid within the skin, a proper formulation has to be developed in further study.

Future Studies

For a better understanding of the storage conditions on the stability, our next research focus will be on the following studies:

a. Comparative study between the shelf life of microscapsules in powdered forms of RP-carnauba wax and RP-beeswax microcapsules in a refrigerator, as well as the stability of the same forms at room temperature.
b. Comparative study between the shelf life of microcapsules in dispersion forms of RP-carnauba wax and RP-beeswax stored 1) in a refrigerator and 2) at room temperature.
c. Study the effect of temperature on the diffusion of active RP core through the shell materials for RP-carnauba wax and RP-beeswax microcapsules of the same forms (powder as well as dispersion) in storage.
d. Conduct release study on water-based formulations of RP-loaded microcapsules using Franz cell diffusion test with a method similar to Salamanca et al. [54] and thus determine the appropriate cosmetic formulation.

Conclusion

This research contributes to the study of stability, release profile, and potentiality of incorporating retinyl palmitate-beeswax microcapsules in facial wipes as a mean to transfer active ingredient to the skin. It was determined from the shelf study that the microcapsules in dispersion form could maintain the active content for 30 days compared to 8 days for the powder form under room temperature. Hence water-based formulations would preserve the stability of the capsules better than the powdered form. The kinetic release study showed that ethanol would accelerate the release of the content. Further study on release in different mediums and storage conditions will help to determine suitable formulation of RP-loaded cosmetics. The simulated transfer study showed

around 22% transfer of RP from non-woven to receptor fabric, thus demonstrated potentials for successful transfer from RP-loaded facial wipes to skin to impart skin-care properties. Future study with appropriate dosage and formulation will contribute to develop innovative cosmeceutical and cosmetotextile products containing retinyl palmitate.

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Declaration of interest

The authors declare no conflict of interest.

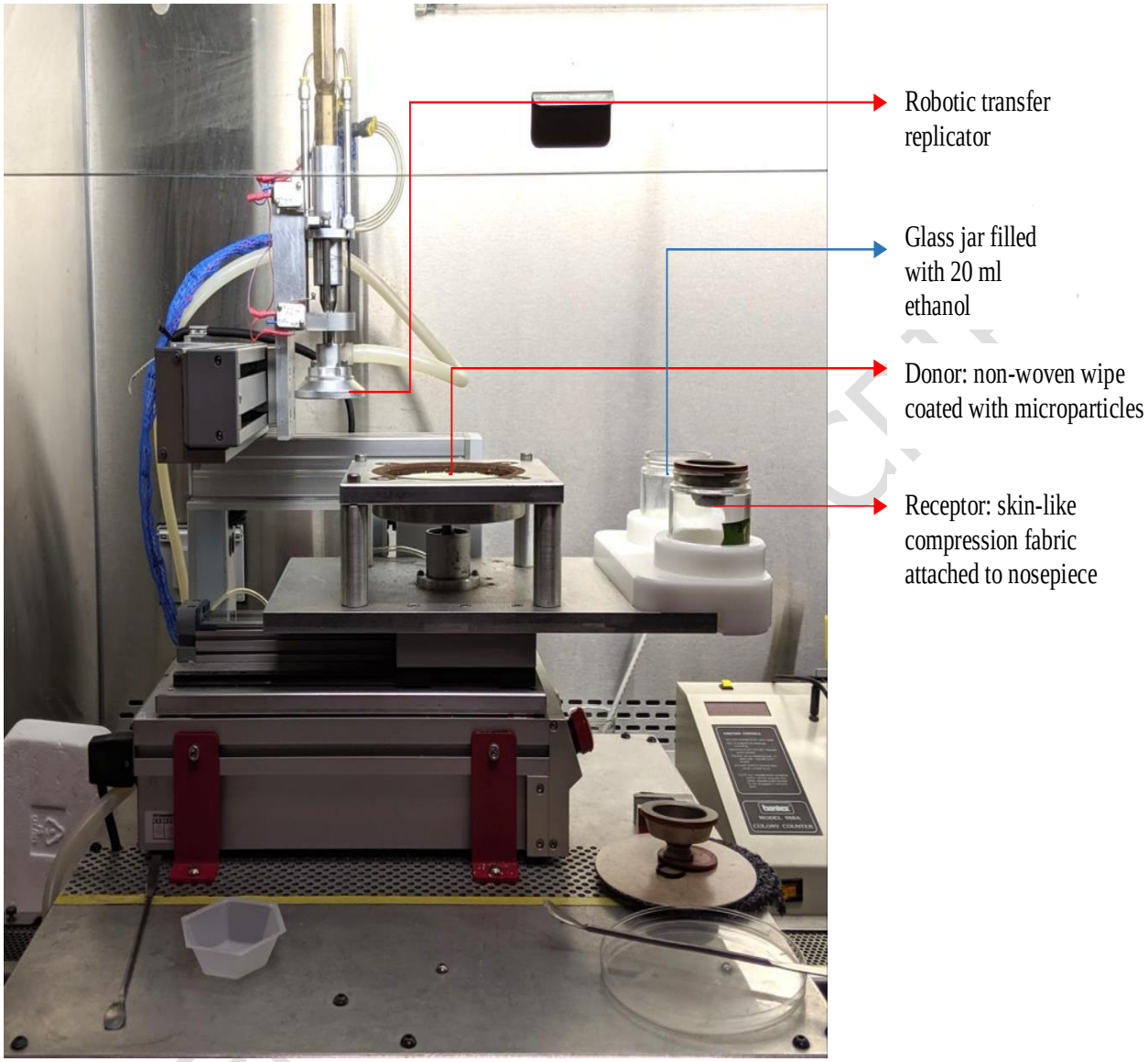

Figure 1: Robotic transfer replicator for simulating the transfer of microparticles from nonwoven wipe to skin-like fabric: Nonwoven moisturizing wipe containing 1 g of microcapsules acted as a donor surface, whereas a compression fabric (warp knit; 77% nylon/ 23% spandex) was the receptor material. The replicator clutched the nose piece and descended the receptor fabric onto the donor surface and rubbed the receptor against the donor by executing programmed motion. After performing this rub cycle, the nose piece was raised and delivered onto a glass jar containing ethanol.

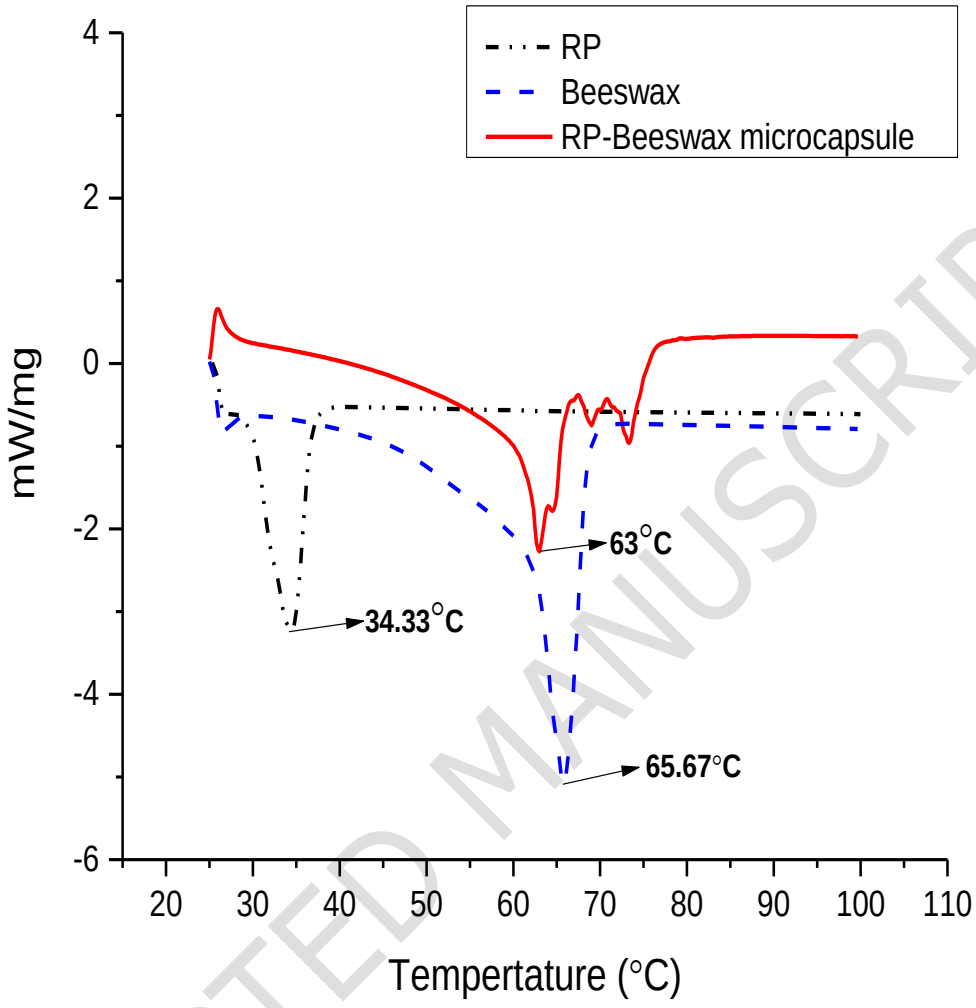

Figure 2: DSC thermogram of untreated beeswax, RP, and RP-loaded beeswax microcapsules (25% w/w theoretical loading capacity): Retinyl palmitate shows a sharp endothermic at 34.33 °C, which corresponds to its melting point. RP-beeswax microcapsules show no endotherms corresponding to the melting point of RP, implying that RP dissolved within the matrix of beeswax when the temperature reached its melting point. Untreated beeswax and RP-loaded beeswax microcapsules showed their melting peaks at 65.67 °C and 63°C, respectively. The slight decrease in the melting point of the particle resulted from the mixing of the RP and the beeswax matrix.

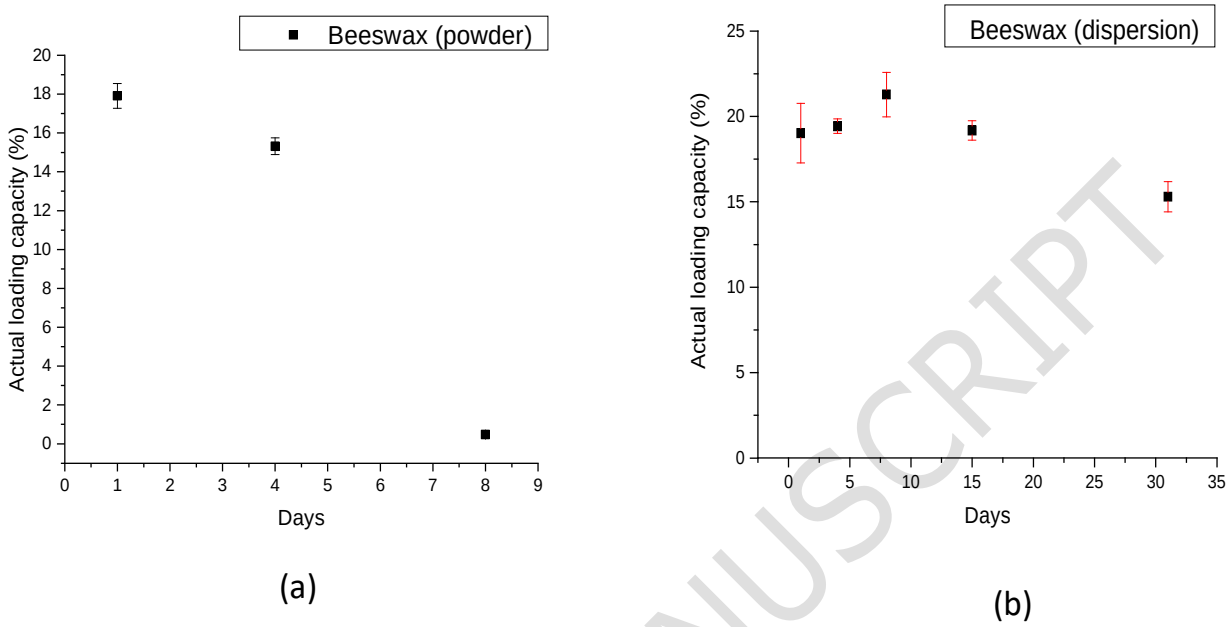

Figure 3: Shelf life study of **(a)** RP loaded beeswax microparticles stored as powder under room temperature **(b)** RP loaded beeswax microparticles stored as a dispersion in a refrigerator. The particles in powder form under room temperature lost their active content within 8 days (a) . The particles stored as disoersion in the refrigerator no significant decrease in RP content until the 15th day (b).

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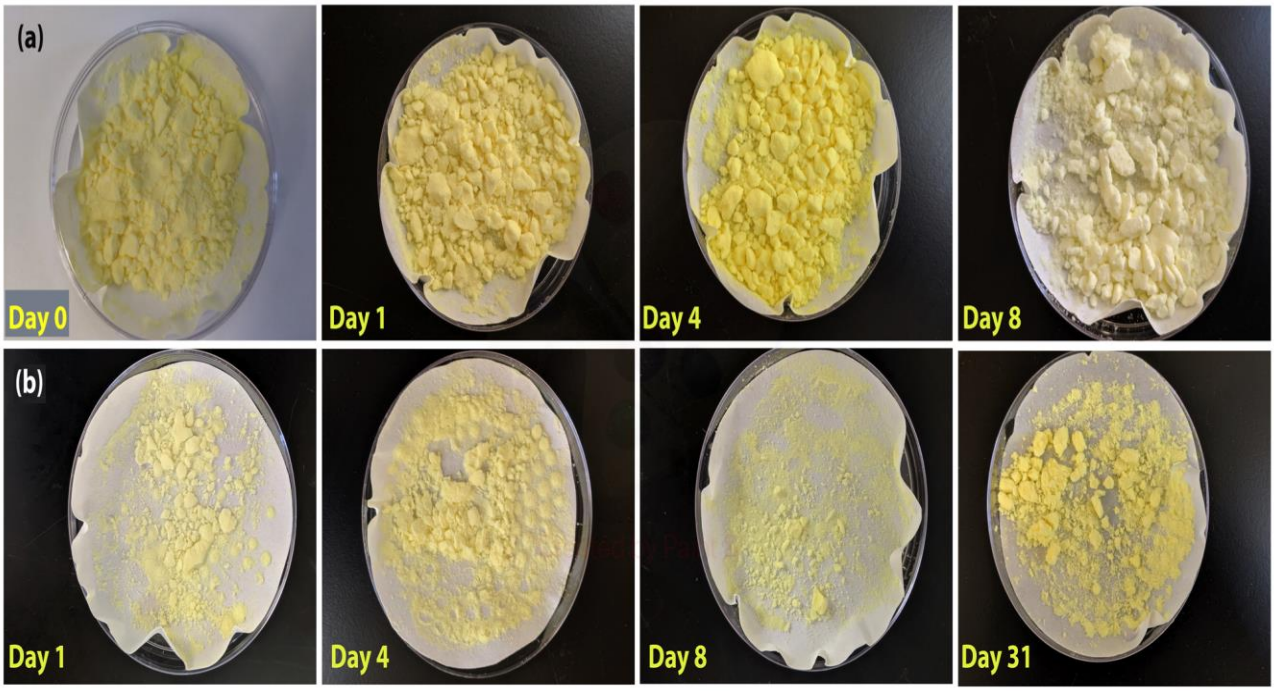

Figure 4: Gradual change in color observed for **(a)** RP-beeswax microparticles stored as powder under room temperature **(b)** RP-beeswax microparticles stored in dispersion.

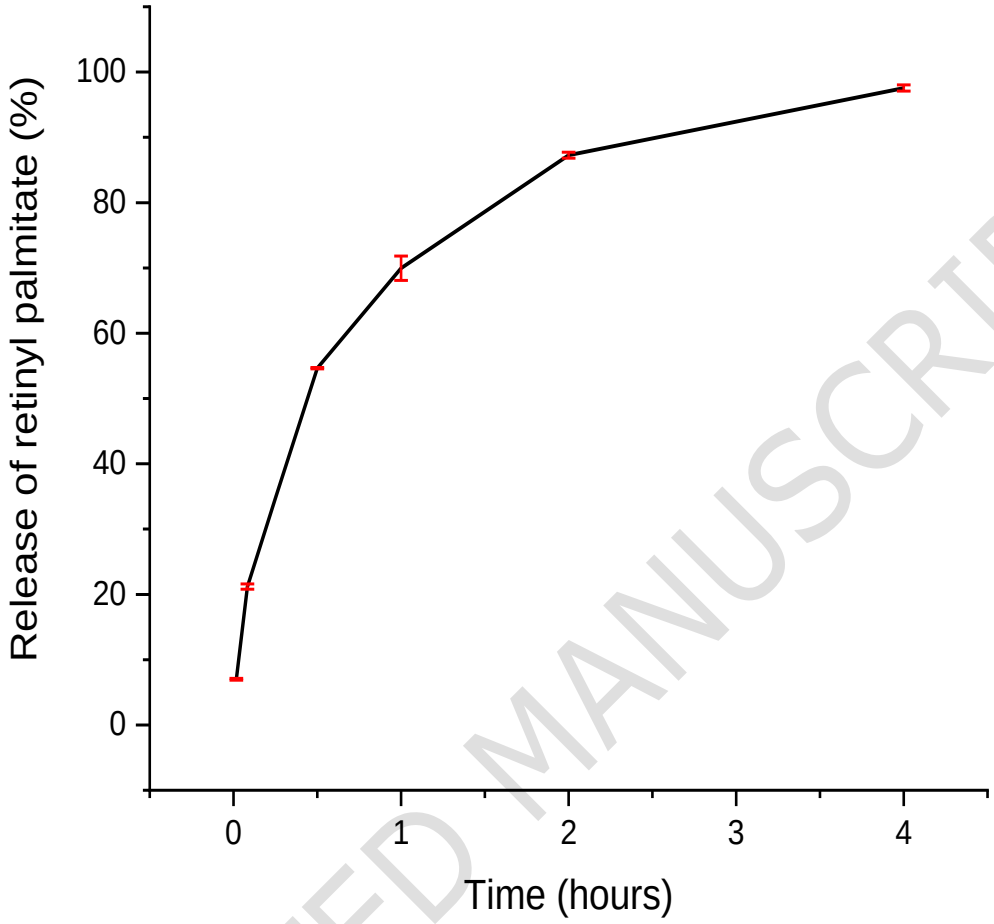

Figure 5: The kinetic release profile of RP-beeswax microcapsules (25% w/w theoretical loading) showed an initial burst followed by a slower release of the vitamin entrapped inside the beeswax matrix. Due to the initial burst effect, 7% of the RP released at the first minute, leading to around 55% release in the first half an hour. After the burst effect, the release profile showed a sustained release over time. Within 4 hours, approximately 98% of RP was released.

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