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Physicochemical properties of macrogol ointment and emulsion ointment blend developed for regulation of water absorption☆

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ABSTRACT

Pressure ulcers can form with excess pressure and shearing stress on skin tissue. Because pressure ulcer is often accompanies by exudates, selection of appropriate topical emulsion ointment is difficult. Blended ointments consisting of emulsion base and water-soluble base are clinically used for adjustment of wound moist environment. Because regulating the amount of wound exudates can enhance treatment efficacy, two new blended ointments were developed. LY–SL blended ointment consisted of lysozyme hydrochloride water-in-oil (w/o) emulsion (LY-cream) and sulfadiazine macrogol (polyethylene glycol) ointment (SL-pasta). TR–SL blended ointment consisted of tretinoin tocoferil oil-in-water (o/w) emulsion (TR-cream) and SL-pasta (TR–SL). LY–SL and TR–SL were applied to Franz diffusion cell with cellulose membranes for the evaluation of water absorption characteristics at 32 °C. Water absorption rate constants ($mg/cm^2/min^{0.5}$) were 12.5, 16.3 and 34.6 for LY-cream, TR-cream and SL-pasta, respectively. Water absorption rate constants for LY–SL and TR–SL (SL-pasta 70%) exhibited intermediate values of 21.2 and 27.2, as compared to each ointment alone, respectively. Because amount of water absorbed was linearly related to square root of time, it was suggested that water-absorbable macrogol was surrounded by oily ingredients forming matrix structure. This diffusion-limited structure may regulate water absorption capacity. This is the first report of physicochemical properties of macrogol ointment and emulsion ointment blend developed for regulation of water absorption. The blended ointment can properly regulate amount of exudates in wounds and may be useful for treatment of pressure ulcers.

1. Introduction

Proper moist environment can promote wound healing. Wound exudates contribute to moist environment. Water-soluble base having water absorption property is used for wounds rich in exudates and emulsion base having water-retaining property is used for wounds poor in exudates (Miyachi, 2009). Use of emulsion base having water-retaining property for wounds rich in exudates can induce excessively moist environment. Conversely, use of water-soluble base for wounds poor in exudates can induce excessively dry environment. Both procedures can retard healing processes. Topical products often used in Japan for treatment of pressure ulcers include LY-cream (Reflap™), TR-cream (Olcenon™) and SL-pasta (Teradia Pasta™). LY-cream is a water-in-oil (w/o) emulsion containing lysozyme hydrochloride (LY) (Yamamoto et al., 1996) and is recommended for promoting granulation tissue in skin ulcers including pressure ulcers. TR-cream is an oil-in-water (o/w) emulsion containing tretinoin tocoferil (TR) (Kawabata et al., 2002). SL-pasta is a macrogol (polyethylene glycol) ointment (MO) containing sulfadiazine (SL) used for treatment of wounds rich in exudates. When emulsion base is used for wounds rich in exudates, one cannot control the amount of exudates. When emulsion base with granulation tissue promoting is blended with SL-pasta with MO base for the treatment of wounds rich in exudates, the blended ointment can properly regulate amount of exudates in wounds, greatly enhancing treatment efficacy (expert opinion, Mizokami et al., 2010).

We have previously established the evaluation method of water absorption capacity of ointment base by using Franz cell model with semi-permeable membranes (Noda et al., 2009). Using this method we have previously reported that water absorption capacity of ointment base is classified based on the mode of absorption. One is an active type, where base can absorb water by osmotic pressure. The

Abbreviations: TR, tretinoin tocoferil; LY, lysozyme hydrochloride; SL, sulfadiazine; BSA, bovine serum albumin; MWCO, molecular weight cut-off; MO, macrogol ointment.

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other is a passive type, where base can absorb water into matrix by diffusion-control (Noda and Fujii, 2010). Using this method we aimed to determine the water absorption characteristics of blended ointments consisting of water-soluble base and emulsion base.

2. Materials and methods

2.1. Materials

LY cream was from Eisai Co., Ltd. (Tokyo, Japan). TR cream was obtained from Kyorin Rimedio Co., Ltd. (Kanazawa, Japan). SL-pasta was from Daiichi Sankyo Co., Ltd. (Tokyo, Japan). These ointments are available in Japan. Components of w/o emulsion base for LY-cream are liquid paraffin, white petrolatum, white beeswax, cetyl palmitate, octyldodecanol, cetanol, stearyl alcohol, paraffin, sorbitan monostearate, polyoxyethylene cetyl ether, polyoxyl (40) stearate, aluminum stearate and D-sorbitol. Components of o/w emulsion base for TR-cream are liquid paraffin, cetanol, polyethylene glycol monostearate, isopropyl myristate, glycerin and D-sorbitol. Components of water soluble base for SL-pasta are macrogol 400 (molecular weight about 400) and macrogol 4000 (molecular weight about 4000). MO is generally mixture of equal amount of macrogol 400 and macrogol 4000. The mixing ratio of other components is not disclosed. Bovine serum albumin (BSA) and cellulose ester membrane were from Wako Pure Chemical Co., Ltd. (Osaka, Japan). The phosphate buffered saline (PBS) was prepared by Mg/Ca ion free Dulbecco's prescription. The simulated wound exudates supplemented with 5% BSA was prepared by Hanks' prescription.

2.2. Methods

2.2.1. Measurement of water absorption rate using Franz diffusion cell

LY cream or TR cream was tempered with appropriate quantity of SL-pasta on a plate to give the blended ointment with contents of SL-pasta adjusted between 0 and 100% on the basis of the total weight. Uniform mixture of the components was achieved by ointment slab and spatula and was visually confirmed. The blended ointment sample (1.2 g) was applied to the cellulose membrane mounted on the Franz diffusion cell (Kawashima et al., 1993; Noda et al., 2009). Twenty mL of simulated wound exudates was introduced to the bellower cell. Molecular weight cut-off (MWCO) values of the cellulose ester membranes used were 100 kDa (Spectrum Laboratories, CA). A water jacket of the permeation cell maintained the system at 32 °C. The temperature was maintained at 32 °C from the respective of the OECD guidance document for the conduct of skin absorption studies. After every 30 min the water level in the branch tube attached to the cell was checked and the simulated fluid was added to the cell from the edge of the branch tube by a syringe until the water level reached its original level. The reduction of syringe weight by adding the simulated fluid was considered equivalent to amount of water absorbed to the ointment sample. Measurements were performed at least 3 times and the means of amount of water absorbed were calculated.

2.2.2. Quantitative analysis of ointment phase separation by ultracentrifugation

Five g of the blended ointments were centrifuged at 25 °C at 16,000 rpm for 1 h by the ultracentrifuge equipment with angle rotor (XL-90, Beckman Coulter, Tokyo, Japan: Vold and Mittal, 1972; Okamoto and Oishi, 1977). The aqueous layer was then collected with a syringe and amount of the aqueous layer was weighed to give the separation ratio of aqueous phase on the basis of the total weight.

2.2.3. Microscopic observation of the dispersed system of blended ointments

The blended ointment was spread out on the glass slides with cover glass. The dispersed system was observed by phase contrast microscopy (IX41, Olympus, Japan).

2.2.4. Assessment of the stability of medicinal properties in the blended ointments

After preparation 10 g of the blended ointments were stored in an ointment container at 25 °C under the dark. Samples were collected at 0, 2, 4 and 24-weeks for determination of the concentration of intact medicinal properties in the blended ointments. The concentration of TR and SL were determined by HPLC analysis. As to LY-cream the residual activities of LY in the blended ointments were assessed by bacterolytic activities against *Micrococcus luteus*. The conditions of HPLC analysis and bacterolytic assay were in accordance with the Japanese Pharmacopeia 14th edition.

2.3. Data analysis

All experiments were performed at least in triplicate. Data are expressed as means ± standard deviations (SDs). Water absorption rate constants were obtained from the slope of the regression line. The differences in the water absorption rate constants of blended ointments were evaluated using Tukey's multiple comparison tests. Probability values of less than 0.05 were considered statistically significant.

3. Results

3.1. Water absorption property of blended ointments used to absorb simulated wound exudates

LY–SL, a blend of LY-cream and SL-pasta, could be prepared in a reproducible fashion except when combination ratio of SL-pasta was 20%, where ointments were separated and could not be prepared.

TR–SL, a blend of TR-cream and SL-pasta, could also be prepared in a reproducible fashion. When combination ratio of SL-pasta was 100%, cumulative amount of water absorbed increased linearly with time and the ointment was completely dissolved in 1 h. When combination ratio of SL-pasta was decreased, ointment was not completely dissolved at 1 h. When amount of water absorbed was plotted against time, the amount of water absorbed per unit of time was reduced. When amount of water absorbed was plotted against the square root of time, a linear correlation was observed at any combination ratio (Fig. 1). If Fickian diffusion is the predominant mechanism of this process, plots of the initial amount of water absorption versus the square root of time should deliver a straight line (Peppas, 1985). Plots of the initial amount of water absorption versus time delivered a curved line, indicating that the rate of water absorption decreases over time. Thus, the water absorption rate constants were obtained from the slope of the regression line of Fig. 1 and used for the comparison of the alterations of water absorbing capacity. The slope of the line became shallow as the ratio of SL-pasta became smaller. The water absorption rate constants of LY-cream, TR-cream and SL-pasta were 12.5, 16.3 and 34.6 ($mg/cm^2/min^{0.5}$), respectively when they were used as single agents (Table 1). The water absorption rate constant calculated from the slope of the lines shown in Fig. 1 was plotted against the combination ratio of SL-pasta (%) (Fig. 2). With LY–SL no significant changes were observed when the combination ratio of LY–SL was within a range of 0–40%, 50–80% and 90–100% (Fig. 2a). There were no significant differences between values at 40% and 50%. Significant differences were observed between values at 0% and 50% ($p < 0.01$), between values at 50% and 90% ($p < 0.01$) and between

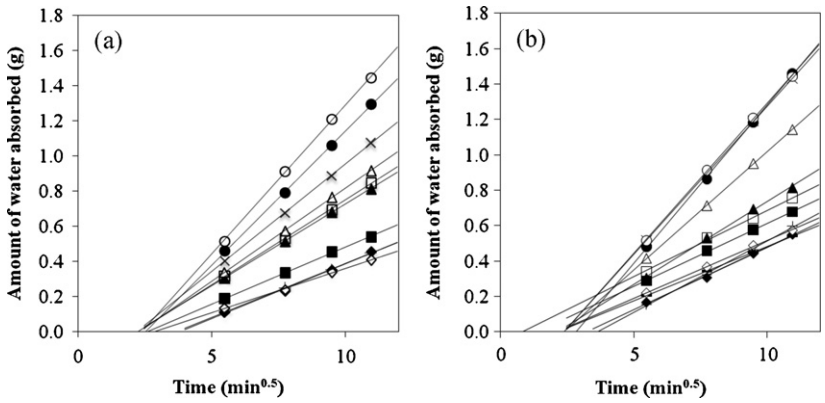

Fig. 1. Total amount of water absorbed into blended ointments evaluated by using 100 kDa MWCO membrane and Hanks' buffer supplemented with 5% BSA. The square root of time was plotted on the *X*-axis and the total amount of water absorbed was plotted on the *Y*-axis. (a) Blended ointment of LY-cream and SL-pasta (LY–SL). (b) Blended ointment of TR-cream and SL-pasta (TR–SL). In (a) and (b) the combination ratios of SL-pasta are expressed as + (0%), ♦ (10%), - (20%), ◊ (30%), ■ (40%), □ (50%), ▲ (60%), △ (70%), × (80%), ● (90%), and ○ (100%). Results are expressed as means ± SD (n = 3–11).

Table 1
Water absorption characteristics of blended ointments.

Combination ratio of SL-pasta (%)	Water absorption rate constant (mg/cm^2/min$^{0.5}$)	
	LY–SL	TR–SL
0	12.5	16.3
50	19.7	15.2
70 (intermediate value)	21.2 (23.6)	27.2 (25.4)
100	34.6	34.6

values at 80% and 90% ($p < 0.05$). With TR–SL the water absorption rate constant was not significantly changed when the combination ratio of SL-pasta was within a range of 0–60% or 80–100% (Fig. 2b). When the combination ratio of SL-pasta was within a range of 60–80%, the water absorption rate constant increased. Significant differences were observed between values at 0% and 70% ($p < 0.01$), between values at 60% and 70% ($p < 0.01$) and between values at 70% and 80% ($p < 0.01$).

3.2. Microscopic analysis of the dispersed system of blended ointments

LY–SL and TR–SL were subjected to microscopic analysis of the dispersed system. With both LY–SL and TR–SL minute phase separation was observed when the combination ratio of SL-pasta was at 30% (Fig. 3). However, when the combination ratio of SL-pasta was at 70%, oil phase was uniformly dispersible in macrogol, suggesting that macrogol formed reticulate structure among oil phase.

3.3. Ultracentrifugal stability of blended ointments

Upon centrifugation clear liquid phase and semisolid phase separated each other in some blended ointments (Fig. 4). Separated liquid phase was sorted to a syringe and weighed. Isolation rate of the liquid phase was calculated and plotted against the combination ratio of SL-pasta (Fig. 5). With 100% LY-cream the separated liquid phase was approximately 10% (Fig. 5a). With LY–SL the separation of liquid phase decreased when the combination ratio of SL-pasta was increased up to 20%. However, the separation of liquid phase increased at the combination ratio of 30%. The separation of liquid decreased again when the combination rate reached 40%. Separation of liquid phase was not virtually observed when the combination ratio was ≥60%. With 100% TR-cream the separated liquid phase was approximately 5% (Fig. 5b). With TR–SL the separation of liquid phase increased even at the low combination ratio of SL-pasta. The separation of liquid phase reached maximum at the combination ratio of 60%. Separation of liquid phase rapidly decreased at the combination ratio of 70% and was not virtually observed when the combination ratio was ≥80%.

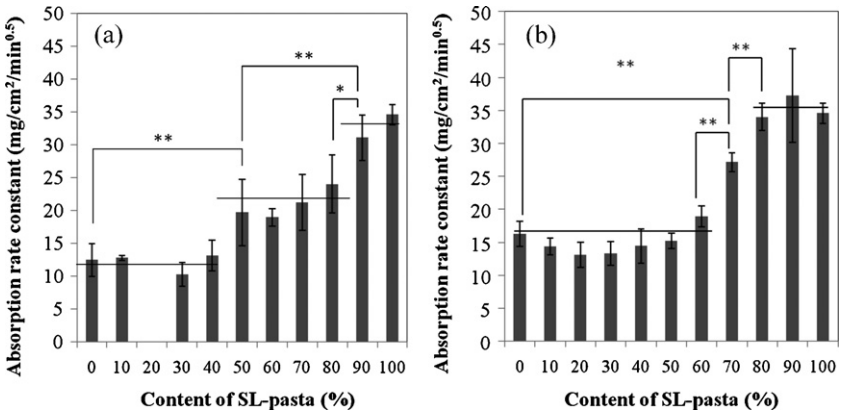

Fig. 2. Water absorption characteristics of blended ointments. The combination ratios of SL-pasta (%) in blended ointments were plotted on the *X*-axis and the water absorption rate constants per unit area obtained from the slop on the line in Fig. 1 were plotted on the *Y*-axis. (a) Blended ointment of LY-cream and SL-pasta (LY–SL). No data was obtained at 20% because of the phase separation on preparation of the blended ointment. (b) Blended ointment of TR-cream and SL-pasta (TR–SL). Results are expressed as means ± SD (n = 3–11). Probability value of less than 0.05 is expressed as *, that of less than 0.01 is expressed as **. Groups without significant differences are indicated with crossbars.

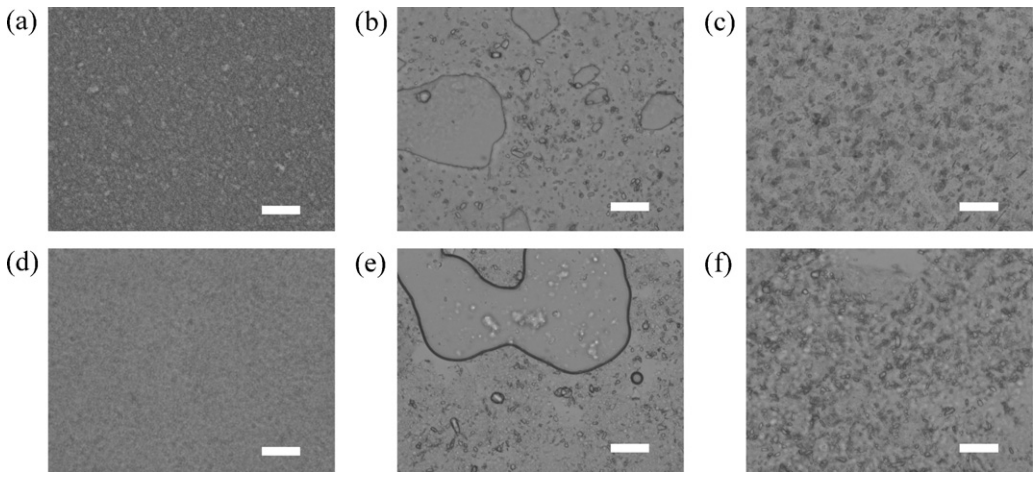

Fig. 3. Microscopic analysis of the dispersed system of blended ointments. Images of LY–SL with combination ratios of SL-pasta at 0% (a), 30% (b) and 70% (c). Images of TR–SL with combination ratios of SL-pasta at 0% (d), 30% (e) and 70% (f). The bars in images indicate 50 μm.

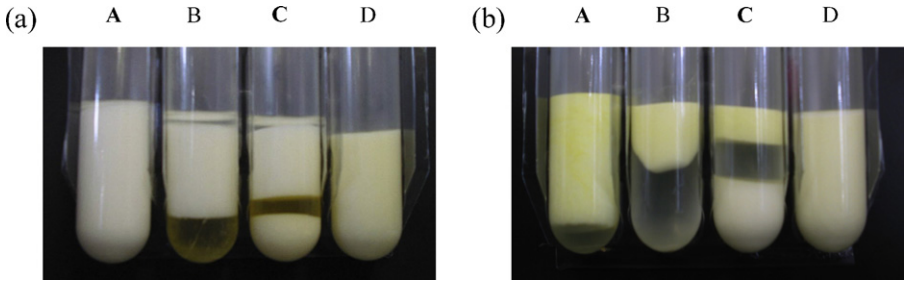

Fig. 4. Representative photographs of separated liquid phases of blended ointments after ultracentrifugation. (a) Blended ointment of LY-cream and SL-pasta (LY–SL). Panels A, B, C and D indicate the combination ratios of SL-pasta at 0%, 30%, 50% and 70%, respectively. (b) Blended ointment of TR-cream and SL-pasta (TR–SL). Panels A, B, C and D indicate the combination ratios of SL-pasta at 0%, 20%, 50% and 80%, respectively.

3.4. Stability of medicinal properties in the blended ointments

With both LY–SL and TR–SL ointments, blended ointments with the combination ratio of SL-pasta at 70% that showed intermediate water absorption characteristics were tested for stability. Upon storage the blended ointments were sampled at 0, 2, 4 and 24-weeks and the % ratios of the residual intact medicinal properties were determined for up to 24 weeks. No significant decreases of residual intact medicinal properties were observed (Fig. 6). Outer appearances were not changed at 24 weeks, either. TR and SL are low-molecular weight organic compounds. On HPLC analysis retention times of basic components were unchanged (data not shown). The amount of remaining lysozyme in blended ointments assessed by bacterolytic activities against *Micrococcus luteus* was not altered, either. Thus, neither chemical alterations of basic components nor biological activities were observed in blended ointment. Therefore, medicinal properties of LY-cream, TR-cream and SL-pasta were stable even after storage of 24 weeks.

4. Discussion

4.1. Mechanisms of water absorption in the blended ointments

Water absorption properties of blended ointments from different lots were tested at least three times. Variabilities of water absorption properties of blended ointments were not greater than those of SL-pasta alone, suggesting that uniform mixture of the components were obtained in a reproducible manner. When water-soluble base (SL-pasta) and emulsion base (LY-cream and TR-cream) were blended, the water absorption rate constant of SL-pasta was decreased. When amount of water absorbed by the blended ointment was plotted against the square root of time, a linear correlation was observed. An analogous linear pattern can be observed when amount of water absorbed by polymer macromolecules is plotted against the square root of time, suggesting that water absorption process of the blended ointment is regulated by diffusion-limited access. As clearly shown in the dispersed system of LY–SL and TR–SL (Fig. 3), when the combination ratio of SL-pasta was at 70%, oil phase was uniformly dispersible in macrogol, suggesting that macrogol formed reticulate structure among oil phase. When water penetrates tortuous macrogol channel, water absorption rate is considered to be decreased. The rate limiting step of water penetration into macrogol channel is the water diffusion into macrogol. This process is similar to the drug release process from matrix. In fact, as the amount of drug release was proportional to square root of time according to Fickian diffusion model (Peppas, 1985), water absorption by blended ointments was proportional to square root of time. When macrogol is dissolved in water, osmotic pressure is produced and active water absorption behavior is observed (Noda and Fujii, 2010). Blended ointments exhibited similar behavior to water absorption into gel. Thus, the water absorption properties of blended ointments are classified as passive water absorption.

LY-cream is a w/o emulsion base and the oil phase serves as the continuous phase. The water content of LY-cream is 21% as measured by dry weight. In blended ointment with 20% SL-pasta the ratio of MO to water was 1 to 1. MO used in SL-pasta is the mixture of equal amount of macrogol 400 (liquid) and macrogol 4000 (solid). MO is semisolid at room temperature and become liquid when dissolved in water. Macrogol 4000 becomes liquid when dissolved in water. Materials with the MO to water ratio of 1 to 1 are liquids. Liquid droplet in emulsion might be swollen to 2 fold by the

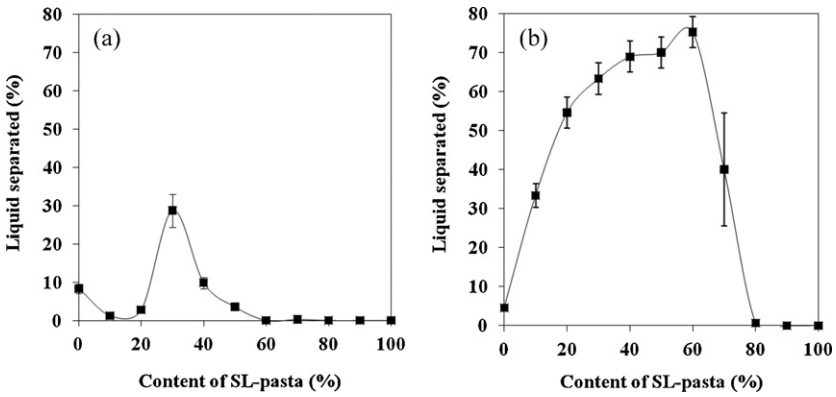

Fig. 5. Centrifugal separation of liquid phase from blended ointments. The combination ratios of SL-pasta (%) in blended ointments were plotted on the *X*-axis and the liquid separated (%) from blended ointments were plotted on the *Y*-axis. (a) Blended ointment of LY-cream and SL-pasta (LY–SL). (b) Blended ointment of TR-cream and SL-pasta (TR–SL). Results are expressed as means ± SD ($n = 3$).

addition of MO and dispersed system was destructed. As a result liquid was separated and the ointment became nonmiscible. It is likely that when amount of MO is increased and exceeds amount of water in the inner phase, water starts to disperse in MO. When amount of MO is increased further, MO begins to retain water and the system is stabilized. Because the blended ointment consisting of MO and w/o emulsion absorbed water in a similar manner with polymer macromolecules, it is likely that MO forms a 3 dimensional reticulate matrix structure.

TR-cream, an o/w emulsion, exhibited similar tendency compared with LY-cream. As to this ointment the oil phase is dispersed as globules throughout an aqueous continuous phase. Because outer phase is water, this ointment base is easily affected by added substances. Upon addition of MO the system became unstable. When substantial amount of MO compared to water in outer phase is added, MO retained water and the system became stable. Oily base surrounds MO and decreased the speed of water entry. As in the case of LY-cream, MO forms a 3 dimensional reticulate matrix structure composed of oily base. The mechanisms of water absorption in these ointments are classified as passive mode.

4.2. Optimization of water absorption capacity of blended ointments

One would have expected that water-soluble base and emulsion base would be blended at 1:1 ratio to obtain an intermediate water absorption capacity. However, changes in water absorption did not correlate with the ratio of MO and LY- and TR-creams (Fig. 2). Rather, changes in water absorption exhibited an intriguing on-and-off phenomenon in a certain range. Water absorption characteristics of blended ointments are summarized in Table 1. With LY–SL at the combination ratio of SL-pasta 70%, the water absorption rate constant of 21.2 ($mg/cm^2/min^{0.5}$) was obtained. This value is similar to the intermediate value between LY-cream and SL-pasta, 23.6. The stability of blended ointment was tested using ultracentrifugation. When the combination ratio of SL-pasta reached 60%, its dispersed system became stable (Fig. 5a). Thus, the combination ratio of SL-pasta at 70%, where its dispersed system became more stable, is appropriate to obtain a blended ointment that shows intermediate water-absorption characteristics between LY-cream and SL-pasta. With TR–SL at the combination ratio of SL-pasta 70%, the water absorption rate constant of 27.2 ($mg/cm^2/min^{0.5}$) was obtained. This value is close to the intermediate value between TR-cream and SL-pasta, 25.4. When the combination ratio of SL-pasta is 60%, the dispersed system was least stable (Fig. 5b). Taken together, to prepare a blended ointment that shows intermediate water absorption capacity between TR-cream and SL-pasta, the combination ratio of SL-pasta around 70% appears reasonable.

4.3. Stability of the blended ointments

Medicinal properties were stable for up to 24 weeks at 25 °C in both blended ointments. TR–SL was less stable in terms of dispersed

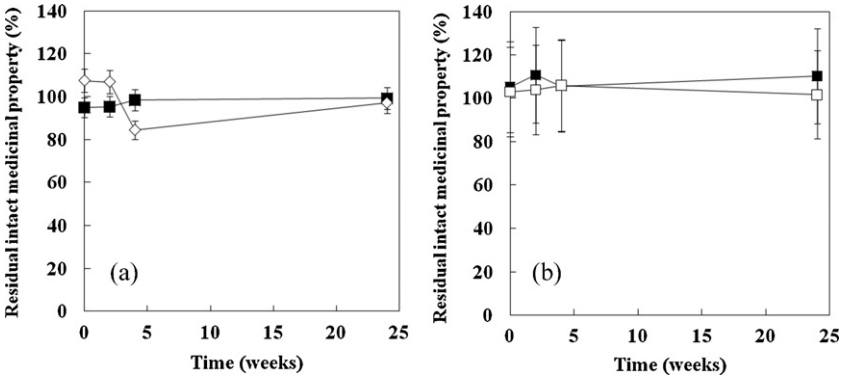

Fig. 6. Stability of the medicinal properties in the blended ointments at 25 °C for up to 24 weeks. Time after the preparation (weeks) was plotted on the *X*-axis and the residual intact medicinal properties in the blended ointment were plotted on the *Y*-axis. Values of the medicinal properties at 0 week were set as 100%. ■ represents SL, ◊ represents LY and □ represents TR.

system as compared to LY–SL and may be prepared only when needed. LY–SL was quite stable in terms of dispersed system and can be stored for substantial periods.

4.4. Strategic use of the blended ointments for pressure ulcers

For the treatment of pressure ulcers MO such as SL-pasta is recommended for wounds rich in exudates (Miyachi, 2009). When MO is used in wounds with less exudate, surface can become dry due to the water absorption capacity of MO and the healing process is greatly delayed. Blended ointments with the combination ratio of SL-pasta 70% with TR–SL or LY–SL are empirically used for wounds with less exudate because they are therapeutically effective. Intermediate water absorption capacity with a blended ointment with SL-pasta 70% may at least partly explain this enhanced therapeutic efficacy.

Ointment base is selected in the light of stability of the medicinal properties. Emulsion base is not considered appropriate for blended ointments because the dispersed system is unstable and liquid phase is likely to be separated. Mixed ointment preparations are often used in dermatology practice. Combinations of multiple ointments are used for dilution of corticosteroids or for adding subsidiary medicinal properties. However, water-soluble base can interfere with emulsion process of emulsion base. Therefore, potential changes in drug release can lead to unexpected adverse effects (Ohtani et al., 2002b).

For the treatment of pressure ulcers ointments are selected to promote wound healing by appropriately adjusting the moist environment. Thus, it is crucial to adjust the water absorption characteristics of the base according to the amount of wound exudates. Although mixed base was previously proposed to improve drug release rate and water absorption for treatment of pressure ulcers (Shigeyama et al., 1999, 2001), the relationship between combination ratio and water absorption capacity remained poorly understood. Regarding physicochemical properties of blended ointments previous studies are limited to evaluating the changes in appearance, the diameters of molecules and phase separation when two ointments are equally admixtured (Ohtani et al., 2002a).

In this study a blended ointment with moderate water absorption capacity was prepared by mixing ointments. When these blended ointments are applied to wound surface of pressure ulcers, it might be possible that the skin permeation of medicinal properties are facilitated (Ohtani et al., 2002b). However, as pressure ulcers do not possess epidermal layers that act as barriers for drug permeability, discussing the facilitation of skin permeation of medicinal properties may not be so meaningful. For treating pressure ulcers blended ointments may regulate the moist environment of wound surface and may facilitate healing. Ointment bases are also considered to regulate cytokine expression on wound surface and facilitate healing (Jae Lee et al., 2007; Mani et al., 2004). This possibility needs further investigation.

5. Conclusion

These two new blended ointments can be prepared in a reproducible manner. They are stable at least for 24 weeks. Their water absorption capacity can be modified depending on the state of the wounds by changing the combination ratio. These physicochemical characteristics may help improve the treatment strategies of pressure ulcers.

Acknowledgements

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