Critical role of water diffusion into matrix in external use iodine preparations

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ARTICLE INFO

ABSTRACT

Iodine preparations for external use are recommended for treating pressure ulcers with manifestations of infection and necrosis. These ulcers abundantly produce wound exudates, which could be absorbed by water-soluble base. In this study we aimed to improve the previously reported methodologies for water absorption and new methodologies were developed in Franz diffusion cell with 100 kDa molecular weight cut-off (MWCO) membranes. Using these new methodologies water absorbing capacities of existing iodine preparations [povidone–iodine (PI) sugar ointment, iodine–potassium iodide (IKI) gel, cadexomer–iodine (CI) ointment] and another superabsorbent polymer dextranomer paste were evaluated. Water absorption indexes were 7.52, 1.98, 1.44 and 2.90 $(mg/cm^2/min^{0.5})$, respectively. With PI sugar ointment observed amount of water absorbed increased in a linear fashion over time. In contrast, with IKI gel, CI ointment and dextranomer paste observed amount of water absorbed decreased over time. When the observed amount of water absorbed was plotted against square of time, the lines of IKI gel and CI ointment became linear. With dextranomer paste the line became biphasic with 1-folding point. These results suggest that water diffusion into matrix is the rate limiting step in IKI gel, CI ointment and dextranomer paste, and that capacity of absorbing wound exudates could substantially differ among these ointments.

1. Introduction

Iodine preparations for external use are recommended for pressure ulcers with manifestations of infection (Miyachi, 2009) and contain iodine for sterilization and water-soluble base for absorbing water. I_2 dissolve sparingly in water and possess irritant and corrosive properties. Iodine complexes such as povidone–iodine (PI) and cadexomer–iodine (CI) have redeeming features. PI is a complex of triiodide ion and polyvinylpyrrolidone and PI sugar ointment with 70% sucrose and 3% PI is widely available as a hospital preparation. PI sugar ointment has been used for pressure ulcer treatment worldwide since 1981 when Knutson et al. reported that the ointment enhanced wound healing (Knutson et al., 1981). When dissolved in wound exudates, it releases triiodide ion and comes to equilibrium with molecular form I_2. CI consists of hydrophilic starch polymer beads that incorporate molecular form iodine. 0.9% CI preparation with macrogol base is widely available (Bianchi, 2001). Upon application to wounds it slowly

releases iodine with swelling of polymer beads induced by exudates (Lamme et al., 1998; Zhou et al., 2002). Although PI sugar ointment and CI ointment have been considered to achieve the same clinical results, we have previously reported that PI and CI ointments exhibit different iodine releasing properties, and that their bases distinctly differ in water absorption capacities (Noda et al., 2009). The amount of molecular iodine released from CI ointment is 9-fold higher than that released from PI sugar ointment when they are dissolved in phosphate buffered saline (PBS). The water absorption rate of PI sugar ointment base is 2-fold higher than that of CI ointment base when one would assume a model of water diffusion into matrix.

Upon treatments with PI sugar ointment or CI ointment one might have some difficulty in removing these ointments from wounds. When these ointments are dissolved in abundant wound exudates, clothes and sheets are sometimes smeared by the iodine. Therefore, workloads of healthcare workers are so high that boosting convenience is desired.

Gel preparation where iodine–potassium iodide (IKI) is dispersed into hydrogel was designed and is readily available in Japan (Hikake et al., 2007). Upon application to wounds it absorbs exudates to form a jelly and slowly releases iodine. With these properties one can easily remove this preparation when wounds are washed. With wound cleansing it also keeps the moist environment and works to prevent infections. Dextranomer beads are

made of a highly hydrophilic dextran polymer in dry form. When dry dextranomer beads in powder-like preparation are placed on a wound, the wound exudates are sucked up into and between the beads. Treatment with dextranomer beads was found to be very effective in cleansing discharging wounds (Jacobsson et al., 1976). Dextranomer paste was invented in Japan to improve adhesiveness of the powder-like material on wound surface, containing no iodine. However, the release kinetics of molecular iodine in water and water absorbance characteristics of base are not fully elucidated with IKI gel and dextranomer paste.

Pressure ulcers with necrotic tissue or manifestations of infection are rich in exudates. Water-soluble base in iodine preparation undertakes a role of absorbing wound exudates. Evaluation methodologies for water absorption of iodine preparations for external use have not been yet established. Furthermore, less expensive generic medicine for PI sugar ointment is available in Japan. Although iodine as medicinal properties may remain the same, base composition may differ depending on the manufacturer. To develop iodine preparation with excellent exudates absorbing capacity, evaluation methodologies for water absorption of iodine preparations for external use must be established.

In this study we aimed to improve the previously reported methodologies for water absorption and new methodologies were developed. Using these new methodologies water absorbing capacities of existing iodine preparations and generic medicines of PI sugar ointment were extensively evaluated.

2. Materials and methods

2.1. Materials

PI sugar ointment (U-PASTA™) was from Kowa Co., Ltd. (Nagoya, Japan). CI ointment (Cadex™ ointment) was from Smith & Nephew Wound Management Corporation (Tokyo, Japan). IKI gel (Iodocoat™) was from Maruho Co., Ltd. (Osaka, Japan). Silicon membrane (thickness 0.10 mm) was from AS ONE Corporation (Osaka, Japan). Dextranomer paste (Debrisan™ paste) was from Sato Co., Ltd. (Tokyo, Japan). Bovine serum albumin (BSA), sodium iodide and seamless cellulose tubing as cellulose membrane were from Wako. Potassium iodide was from Nacalai Tesque, Inc. (Kyoto, Japan). Starch was from Kenei Pharmaceutical Co., Ltd. (Osaka, Japan). The phosphate buffered saline (PBS) was prepared by Mg/Ca ion free Dulbecco's prescription. The simulated fluid supplemented with 5% BSA was prepared by Hanks' prescription.

2.2. Methods

2.2.1. Measurement of water absorption rate using Franz diffusion cell

The 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) and 20 mL of simulated fluid was introduced to the bellower cell. Molecular weight cut-off (MWCO) values of the cellulose membranes used were 100 kDa. A water jacket of the permeation cell maintained the system at 32 °C. After every 15 or 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 the amount of water absorbed to the ointment sample. Measurements were performed at least 3 times and the means of the amount of water absorbed were calculated.

2.2.2. Electron microscopic observation of the surface of polymer beads

CI ointment and dextranomer paste were allowed react with 1% sodium thiosulfate solution for 10 min at room temperature, respectively. The residue was washed with distilled water 3 times and dried. The dried polymer beads were observed by scanning electron microscope (JSM-6060LK, JEOL Ltd., Tokyo, Japan).

2.2.3. Assessment of the concentration of free-iodine in the aqueous solution

Apparent permeability of iodine has been found to depend on the activity of iodine in aqueous solution (Takikawa et al., 1978). For measurement of permeability of iodine through silicon membrane, a permeation cell commercially available was employed. The permeation cell consisted of two compartments with a silicon membrane between them. The area of membrane for permeation was 4.91 cm^2. Each compartment was agitated by a magnetic stirring bar. A test solution (25 mL) and 10% NaI solution were placed in the donor and the receptor compartments, respectively. A water jacket of the permeation cell maintained the system at 30 °C. Samples (1 mL) were pipetted from the receptor solution, and assayed spectrophotometerically at 352 nm employing a spectrophotometer.

2.3. Data analysis

All experiments were conducted at least in triplicate. Data are expressed as means ± SDs. In experiments of water absorption, water absorption rate constants were obtained from the slope of the regression line in the same manner.

3. Results

3.1. Modification of the assay system for water absorption of ointment

Water absorbance characteristics of PI sugar ointment and macrogol ointment were characterized as previously described (Noda et al., 2009) using the Franz diffusion cell. Initially, the ointment sample (1.2 g) was applied to the 14 kDa MWCO membrane and 20 mL of PBS was introduced to the bellower cell. With both PI sugar and macrogol ointments the amount of PBS absorbed increased in a linear manner (Fig. 1a). Both preparations dissolved in 60–75 min. The slopes of the line corresponded with each other.

Next, to simulate more physiological conditions PBS in the bellower cell was replaced with Hanks' buffer containing 5% BSA, which is more similar to tissue fluid. As wound exudates of pressure ulcer contain approximately 5% protein (Noda et al., 2009) the 14 kDa MWCO membrane was changed to BSA-permeable 100 kDa MWCO one. Both PI sugar ointment and macrogol ointment dissolved in 30–45 min. After dissolution water absorbance still increased linearly. The slope of PI sugar ointment was greater than that of macrogol ointment (Fig. 1b). Based on the slope of the line water absorption rate constant per unit area was determined. The water absorption rate constant per unit area of marogol ointment was 71% of that of PI sugar ointment, which contains not only macrogol but also sucrose (Table 1). Water absorbance characteristics of PI sugar ointment and macrogol ointment were characterized using Hanks' buffer with or without 5%BSA. The presence or absence of 5% BSA did not affect water absorbance characteristics (results not shown).
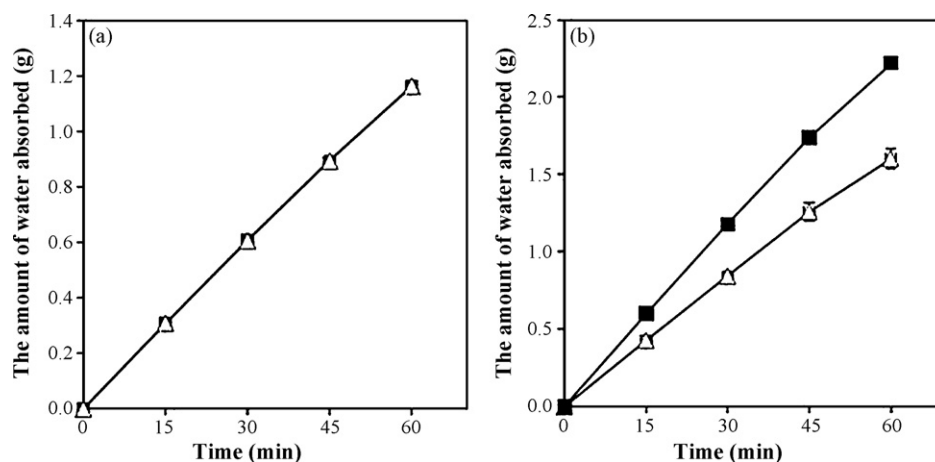
Fig. 1. Total amount of water absorbed into ointments versus time, using 14 kDa MWCO membrane and PBS (a), and using 100 kDa MWCO membrane and Hanks' buffer supplemented with 5% BSA (b). PI sugar ointment is expressed as closed square and macrogol ointment is expressed as open triangle. Results are expressed as means ± SD ($n = 3$).

Table 1

Water absorption characteristics of ointments, obtained by existing assay system and modified assay system.

	Water absorption rate constant per unit area (mg/cm^2/min)[a]	
	Existing system	Modified system
PI sugar ointment	3.96	7.52
Macrogol ointment	3.96	5.43

[a] Value of a slope obtained from the regression line in Fig. 1.

Table 2

Water absorption characteristics of ointments used for eliminating wound exudates.

| Test ointment	Water absorption rate constant per unit area (mg/cm^2/min$^{0.5}$)[a]	Water absorption index[b]
PI sugar ointment	7.52	1.00
IKI gel	1.98	0.26
CI ointment	1.44	0.19
Dextranomer paste	2.90	0.39

[a] Value of a slope obtained from the regression line in Fig. 2b.

[b] Ratio of the water absorption rate constant per unit area of test ointment versus that of PI sugar ointment.

3.2. Water absorption property of ointments used to absorb wound exudates

Water absorption characteristics of ointments, which absorb wound exudates, such as PI sugar ointment, CI ointment, IKI gel and dextranomer paste, were determined. With PI sugar ointment observed amount of water absorbed increased in a liner fashion over time (Fig. 2a). In contrast, with dextranomer paste, IKI gel and CI ointment observed amount of water absorbed decreased over time. When the observed amount of water absorbed was plotted against square of time, the lines of IKI gel and CI ointment became linear (Fig. 2b). With dextranomer paste the line became biphasic with 1-folding point. From the slope of the regression line of the linear portion of each graph, the apparent water absorption rate constant per unit area was calculated. The ratio of the water absorption rate constant per unit area of test ointment versus that of PI sugar ointment was defined as the water absorption index. CI ointment, IKI gel and dextranomer paste have a water absorption mechanism clearly different from that of PI sugar ointment and that water absorbance is decreased by more than 60% (Table 2).

3.3. Scanning electron microscopic analysis of the surface of polymer beads

The morphological characteristics of the surface of cadexomer beads and dextranomer beads were evaluated using scanning elec-
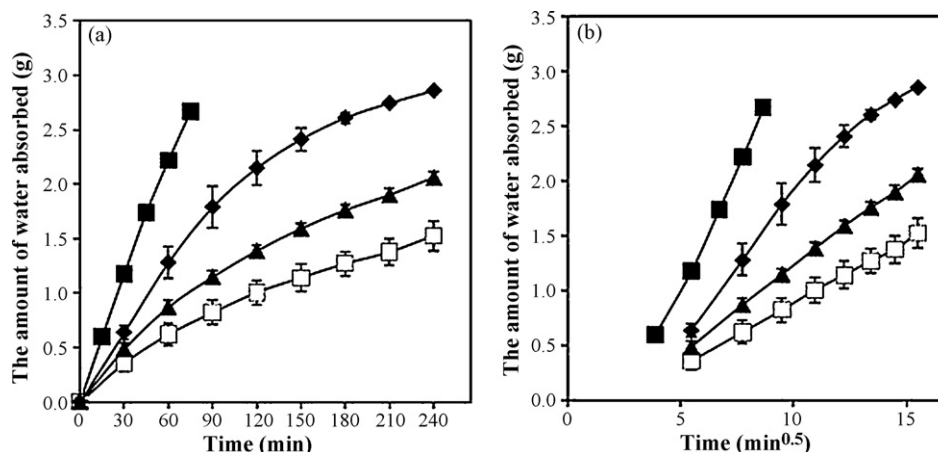
Fig. 2. Total amount of water absorbed into ointments using 100 kDa MWCO membrane and Hanks' buffer supplemented with 5% BSA (a). The square root of time was plotted on the X axis and the total amount of water absorbed was re-plotted on the Y axis (b). PI sugar ointment is expressed as closed square, CI ointment is expressed as open square, IKI gel is expressed as closed triangle and dextranomer paste is expressed as closed diamond. Results are expressed as means ± SD ($n = 3$).
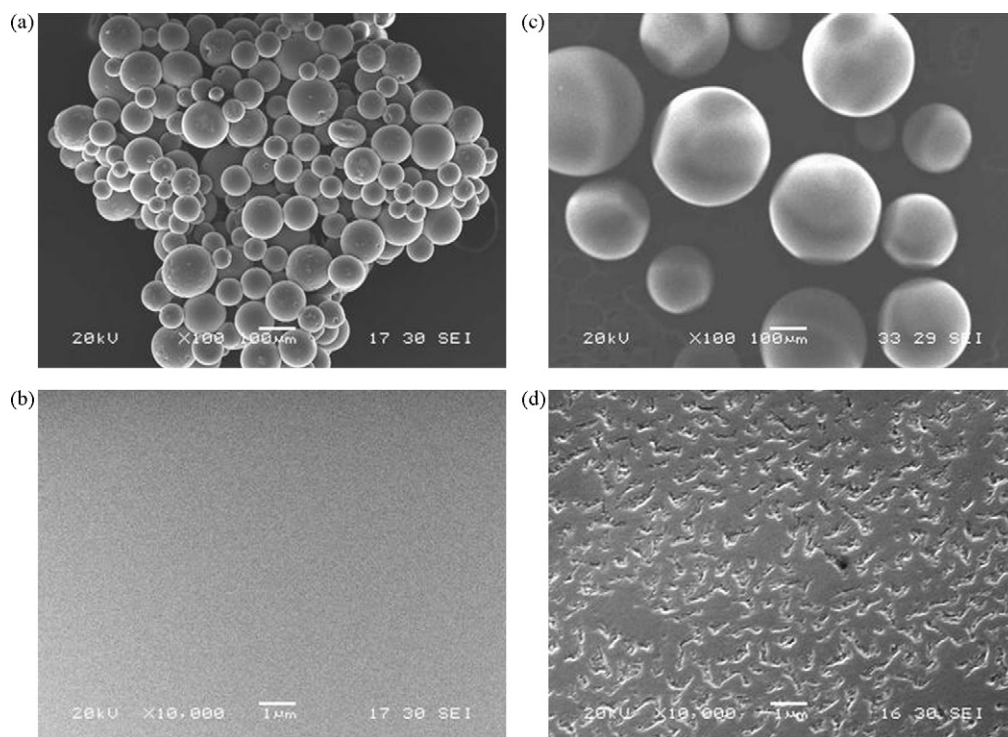
Fig. 3. Scanning electron microscopic image of surface of polymer beads. Observed image of cadexomer beads ×100 (a), cadexomer beads ×10,000 (b), dextranomer beads ×100 (c), and dextranomer beads ×10,000 (d). The bar in (a and c) indicates 100 mm. The bar in (b and d) indicates 1 mm.

tron microscope. The cadexomer beads exhibited global shape with 50–100 μm of diameter (Fig. 3a) and the surface was smooth (Fig. 3b). The dextranomer beads exhibited global shape with 150–300 μm of diameter (Fig. 3c). The surface was porous with numerous cleavage of approximately 1 μm (Fig. 3d).

3.4. Water absorption property of 6 preparations of generic medicine of PI sugar ointment

PI sugar ointment is one of the heavily used preparations in Japan for treatment of pressure ulcers. Because PI sugar ointment is rather expensive, similar pharmaceutical compounds in generic forms are often used. With generic products medicinal properties remain the same. However, ointment base can vary from

manufacturer to manufacturer. Appropriate moist environment is required for treatment of pressure ulcers and ointment base can critically affect the moist environment of wounds (Miyachi, 2009). Thus, one needs to evaluate the water absorption property of various preparations of generic medicine of PI sugar ointment. Water absorption characteristics of 6 preparations of generic medicine (namely G1–G6) of PI sugar ointment were determined. Original drug PI sugar ointment had the highest amount of water absorbed (Fig. 4a). With G6 more than 10% reduction was observed when pH of the simulated fluid was 7.3. When the pH of simulated fluid was changed to 6.8, all generic medicine except G5 exhibited reduced amount of water absorbed (Fig. 4b). In particular G2 and G6 exhibited marked reduction of water absorbing capacity (Table 3). The ratio of the water absorption rate constant per unit area of test
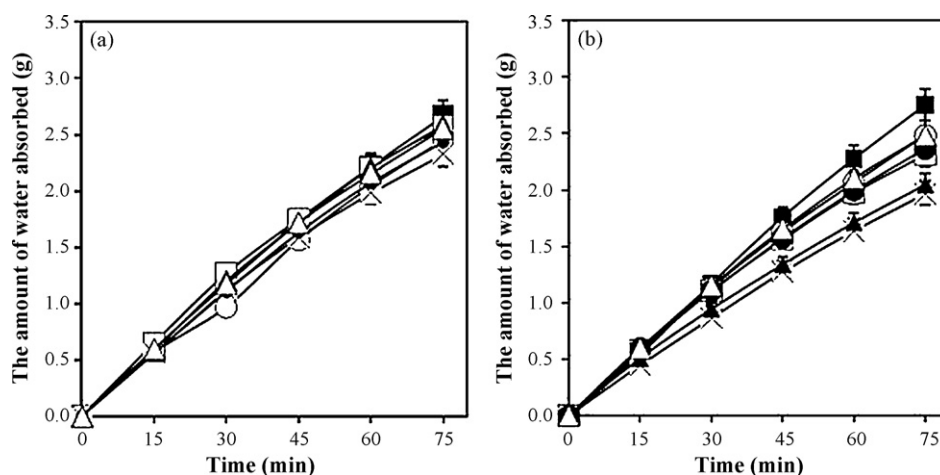
Fig. 4. Total amount of water absorbed into ointments of generic medicine of PI sugar ointment. The simulated fluids was prepare at pH 7.3 (a) and at pH 6.8 (b). Original PI sugar ointment is expressed as closed square, G1 is expressed as open square, G2 is expressed as closed triangle, G3 is expressed as open triangle, G4 is expressed as closed circle, G5 is expressed as open circle, and G6 is expressed as the × mark. Results are expressed as means ± SD ($n = 3$).

Table 3
Water absorption characteristics of ointments and pH values of preparation dissolved in saline, a series of generic drugs of PI sugar ointment.

PI sugar ointment	pH 7.3		pH 6.9		pH value of preparation dissolved in saline[c]
	Water absorption rate constant per unit area (mg/cm^2/min$^{0.5}$)[a]	Water absorption index[b]	Water absorption rate constant per unit area (mg/cm^2/min$^{0.5}$)[a]	Water absorption index[b]	
Original	7.52	1.00	7.67	1.01	4.93
G1	7.46	0.99	6.67	0.89	5.14
G2	7.40	0.98	5.82	0.77	5.05
G3	7.30	0.97	7.11	0.95	4.98
G4	6.96	0.93	6.76	0.90	5.17
G5	6.85	0.91	7.03	0.93	5.16
G6	6.72	0.89	5.54	0.74	5.04

[a] Value of a slope obtained from the regression line in Fig. 2b.
[b] Ratio of the water absorption rate constant per unit area of test ointment versus that of original PI sugar ointment in pH 7.3.
[c] pH value of saline was 5.32.
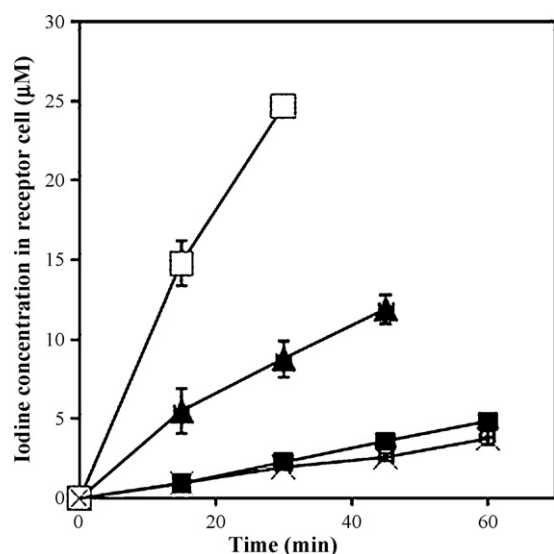
Fig. 5. Permeation patterns of free-iodine (initial total iodine concentration, 0.1%) through the silicone membrane at 30 °C. PI sugar ointment is expressed as closed square, IKI gel is expressed as closed triangle, CI ointment is expressed as open square and G6 is expressed as the × mark. Results are expressed as means ± SD (n = 3).

ointment versus that of PI sugar ointment was defined as water absorption index. When pH of the simulated fluid was 7.3, there were no major differences as compared to the original drug PI sugar ointment. With G6 more than 10% reduction was observed. When the pH of simulated fluid was changed to 6.8, 5 generic medicine exhibited reduced amount of water absorbed. In particular G2 and G6 exhibited reduction of water absorbing capacity by 23% and 26%, respectively (Table 3). Seven preparations of PI sugar ointments including the original drug were dissolved in saline and their pH values were determined. The pH values of these preparations indicated almost equivalent values in the range between 4.9 and 5.2 (Table 3).

3.5. Estimation of free-iodine concentration by iodine permeation assay through the silicone membrane

As we previously reported (Noda et al., 2009), the rate of increase of iodine concentration in the receptor compartment was assumed to be in proportion to the iodine concentration in the donor compartment. The permeability of iodine through silicon membrane with a thickness of 0.1 mm, a permeation cell commercially available was measured at 30 °C. Concentration of iodine in the receptor compartment increased linearly over time (Fig. 5). As we previously reported (Noda et al., 2009), the rate of increase of iodine concentration in the receptor compartment was assumed to be in proportion to the iodine concentration in the donor compartment. The slope of the graph reflects the permeability speed of the free-iodine. When CI ointment was dissolved in PBS, iodine concentration of the supernatant was 1.2 mM. Thus, the free-iodine concentration released into fluid from CI ointment was put as 1.2 mM and the free-iodine concentration released from each ointment was estimated. The free-iodine concentration released into fluid was the highest with CI ointment among the 4 ointments tested. The value was 11-fold higher than the value with PI sugar ointment consistent with our previous report (Noda et al., 2009). The values with IKI gel and G6 were 3.6-fold and 0.8-fold higher than the value with PI sugar ointment, respectively (Table 4).

4. Discussions

4.1. Modification of the assay system for water absorption of ointment

Changing simulated fluid from PBS to Hanks' buffer with 5% BSA and MWCO of the cellulose membranes from 14 to 100 kDa enabled us to distinguish the differences in water absorption properties between PI sugar ointment and macrogol ointment. Both PBS and Hanks' buffer are isotonic and their ionic strength and pH are similar. When water absorbance characteristics of PI sugar ointment and macrogol ointment were characterized using Hanks' buffer with or without 5%BSA, the presence or absence of 5% BSA did not affect water absorbance characteristics, suggesting that the

Table 4
Permeation rate of free-iodine through silicon membrane.

Test ointment	Observed permeation rate of free-iodine (A.U.)	Estimated concentration of free-iodine in donor cell (mM)
CI ointment	0.85	1.20
IKI gel ointment	0.28	0.40
Original PI sugar ointment	0.079	0.11
G6 (PI sugar ointment)	0.062	0.088

distinction of the two preparations could be due to the membrane and not due to simulated fluid. The slope of the graph was in proportion to the amount of water absorbed per unit of time. Because the diameter of the cell or the amount of ointment loaded to the cell remains the same, one can estimate the water absorption rate constant per unit area by comparing the magnitude of the slopes. PI sugar ointment may have exhibited higher water absorption properties than macrogol ointment as the molecular weight of sucrose present in PI sugar ointment is smaller than that of macrogol and hence has more osmotic pressure effect than macrogol.

4.2. Water absorption property of ointments used to absorb wound exudates and its determinants

4.2.1. Water absorption property of ointments used to absorb wound exudates

PI sugar ointment with water-soluble base was dissolved in absorbed water. Because water absorption rate constant per unit area was unchanged even after PI sugar ointment is dissolved, osmotic pressure may be the main force to absorb water in PI sugar ointment.

With IKI gel, CI ointment and dextranomer paste observed amount of water absorbed decreased over time. When the observed amount of water absorbed was plotted against square of time, the lines of IKI gel and CI ointment became linear, suggesting that they absorb water when a model of water diffusion into matrix is assumed. To evaluate the water absorbance properties it was assumed that these ointments possessed the same mechanism of action and water absorbance rate constant was calculated by the slope of the line in Fig. 2b. With IKI gel, CI ointment and dextranomer paste water absorption rate constant per unit area gradually decreased over time and reached plateau after several hours. IKI gel is a hydrogel of carmellose Na and polyacrylic acid Na. This material is superabsorbent polymers and water absorption takes place by diffusion of water into three-dimensional lattice and are dispersed into macrogol ointment. In dextranomer paste and CI ointment dextranomer beads and cadexomer beads are dispersed as absorbent polymer beads into macrogol ointment, respectively. Water is sucked into and between polymer beads (Jacobsson et al., 1976) and the water absorption takes place by diffusion of water into three-dimensional lattice.

Dextranomer has three-dimensional lattice with cross-linking dextran, and cadexomer has a similar structure with three-dimensional lattice with cross-linking dextrin. On electron microscopic analysis (Fig. 3) dextranomer beads had numerous micropores and cadexomer beads had a smooth surface. Because a granule is defined as porous matrix rather than homogenous one, drug release from granular matrix is expressed by Higuchi equation where the opening in the matrix is taken into serious consideration (Chandrasekaran and Hillman, 1980). Drug release from granular matrix involves the simultaneous penetration of the surrounding liquid so that the rate of release is increased due to pores. Therefore, the penetration of the surrounding liquid is enhanced due to pores on the surface of polymer beads similar to granules. When water makes contacts with the beads, water infiltrates dextranomer beads through micropores and rapid water absorption takes place. In contrast, cadexomer beads absorb water by surface permeation through gel swelling. These differences may have caused substantial variations in water absorption rate constant. Furthermore, with dextranomer beads water continues to be absorbed through gel swelling when absorption through micropore reaches plateau. These changes may have contributed to the biphasic nature of the water absorption line on Fig. 2b. Indeed, the fact that the slope of the second phase line of dextranomer paste is in parallel with the slope of the line of CI ointment strongly supports this view.

4.2.2. Determinants of water absorption properties

With sucrose and low-molecular weight macrogol osmotic pressure is increased when PI sugar ointment is placed on semipermeable membranes and is dissolved in small amount of water and absorbs water. Osmotic pressure is barely induced with hydrogel and polymer beads. When polymer beads dextranomer was placed on semipermeable membranes, no water absorption was observed. With dextranomer paste low-molecular weight macrogol in the base can induce osmotic pressure and can absorb water through semipermeable membranes. Polymer beads absorb over-flown water. In granulation tissue of pressure ulcers water absorption through osmotic pressure is an active process. This mode of absorption may dehydrate edematous granulation tissue and wound edema may be improved. Water absorption in a passive manner through hydrogel and polymer beads can absorb and retain extra-vascular fluid. This process may remove excess wound exudates from pressure ulcers while keeping the surface moist.

4.3. Water absorption property of 6 preparations of generic medicine of PI sugar ointment

Water absorption characteristics of 6 preparations of generic medicine (G1–G6) of PI sugar ointment were quite variable. Although iodine as medicinal properties may remain the same, base compositions may quite differ depending on the manufacturer. When the types of characteristic additives were compared, G2 contains carboxyvinyl polymer and G6 contains sodium alginate. These additives are carboxylic acid with –COOH group. Carboxylic acid is a weak acid and undergoes dissociation and stay at ionic and soluble form at neutral and alkaline range. However, at acidic range, molecular form predominates and becomes poorly soluble. Thus, it is likely that addition of carboxylic acid may have decreased the water absorbance capacity. Because G5 contained sodium alginate as well, differences in compounding ratio and other additives may have contributed to different water absorption pattern of G5 as compared to G6.

When PI sugar ointment was dissolved in physiological saline at 1:1 ratio, the pH of the solution was approximately 5.0. When PI sugar ointment is dissolved in a solution, the pH of the solution is maintained by the buffer used. If the buffering functions of wound exudates are small when PI sugar ointment is used to treat pressure ulcers, local pH may be decreased. In fact, low pH may exert favorable effects on wound-healing (Schneider et al., 2007). Thus, most of the agents used for pressure ulcer treatment are prepared to decrease local pH. When the pH of simulated fluid was changed to 6.8, all generic medicines except G5 exhibited reduced amount of water absorbed. These generic medicines of PI sugar ointment may exhibit decreased active water absorption when they are applied to pressure ulcers due to low local pH. Reduced water absorption may unfavorably affect the treatment outcomes. Ointment preparations may be exposed to local low pH on the semipermeable membranes when they are exposed to simulated fluid. The acidic environment may affect water absorbance characteristics. Thus, use of physiological saline or Ringer's solution may help presume the water absorption characteristics in wound granulation tissues (Shigeyama et al., 2001).

4.4. Release patterns of free-iodine

Ointments were dissolved in PBS (pH 7.3) and concentration of free-iodine released into the fluid phase was estimated. free-iodine's targets are located in the bacterial cytoplasmic membrane, and its killing action takes place in a matter of seconds (Rodeheaver et al., 1982). Free-iodine reacts with cell membrane of wound tissue and may seriously damage surrounding cells (Jose, 1986). PI sugar ointments release I_3^- and I_3^- may be held in equilibrium

with I_2 and I^-. IKI gels also release I_3^- and I_3^- may be held in equilibrium with I_2 and I^-. In contrast, I_2 released from CI ointment is more lipophilic than I_3^- and is distributed to cellular lipid membranes. Because reactivity with lipids depends on iodine concentration (Noda et al., 2009), preparations with high releasing capacity of free-iodine may have both high bactericidal action and cellular toxicity.

5. Conclusion

This study showed that the water absorption properties and release pattern of free-iodine vary widely among the external use iodine preparations examined, suggesting that free-iodine concentrations in pressure ulcers on site may vary widely when iodine preparations are clinically applied and exposed to wound exudates. Careful quantitative comparisons of water absorption properties and release patters of free-iodine will help properly evaluate iodine preparations. The methodologies we have developed will be useful for quality evaluations of iodine preparations including generic medicine.

Acknowledgements

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