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Drug Release Test to Assess Quality of Topical Formulations in Japanese Market

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ABSTRACT

Three release test methods—watch glass method, rotating dialyses cell method, and disk assembly method (DA)—were assessed for use in a quality control procedure for four different semisolid topical formulations containing indomethacin (IDM). Although minor modification in the methods to optimize the release rate was necessary for each formulation, DA proved superior to the other two methods and thus was used to assess the quality of topical formulations on the Japanese market. First, DA was used for a storage test of hydrophilic ointments and cataplasms; difference in the release profiles of IDM from these formulations showed changes with time, which suggests the usefulness of DA for checking lot-to-lot uniformity. Second, dermal patch and tape as transdermal delivery systems containing nitroglycerin or isosorbide dinitrate were investigated. Since different sizes and shapes of these products are available, various assemblies of DA were required to fit individual products. Different release patterns were obtained among the products for both drugs. These results suggest that DA is a simple, reproducible, and more useful quantitative release test for quality control of topical formulations.

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INTRODUCTION

Dermal patches and tapes for transdermal delivery systems (TDS) to achieve systemic effects—in addition to ointments, creams, and cataplasms expected to provide topical therapeutic effects—have appeared on the Japanese market. Various new products are expected to be developed in the future, but a standard method is not yet available to assess the quality and ability (or performance) of the topical formulations.

Dissolution tests for oral dosage forms have already been established as "official" methods (1,2). Oral dosage forms disintegrate and pharmacologically active ingredients dissolve in the gastrointestinal tract before absorption of the ingredients into the systemic circulation after their administration. In sustained-release oral formulations, the absorption rate of a drug can be predicted by its dissolution rate. For a topical preparation, disintegration may correspond to contact of a vehicle with the stratum corneum, the uppermost layer of skin, because a drug can begin to penetrate into skin from the vehicle immediately after contact. Percutaneous absorption rate of a drug is generally lower than its release rate from a topical formulation due to the markedly high barrier posed by the stratum corneum to passage of the drug: the release rate of a drug therefore does not always reflect the absorption rate (3). Whenever effectiveness is dependent on the release of a drug from a vehicle, however, determination of the release rate is important for controlling the quality of the product (4). Although the U.S. Food and Drug Administration (FDA) has developed release testing procedures for TDS (1), these procedures do not always apply to all products. FDA proposed the watch glass method for patches and the Franz cell method for semisolid vehicles such as ointments and creams (5,6). These apparatuses are on the market in the United States and Japan, but there are problems in conducting the release test using certain formulations.

This paper describes release test methods to assess the quality of topical formulations on the Japanese market. Most of the test apparatus was Japanese Pharmacopoeia (JP XII) dissolution apparatus (2). Formulations tested in this study were four semisolid topical formulations containing indomethacin (IDM) as a model drug and several products marketed in Japan: cataplasms, patches, and tapes.

MATERIALS AND METHODS

Drug and Dosage Forms

IDM (JP grade) was selected as a model drug. Gel was prepared using 5% (w/w) hydroxypropylcellulose (150–400 cps, Wako Pure Chemical Ind., Ltd., Osaka, Japan). Hydrophilic ointment and simple ointment were prepared according to JP XII. Petrolatum ointment was prepared by a melting method. These semisolid formulations contain 0.7%, 1.0%, or 1.3% IDM. Two cataplasms containing 0.75% IDM (Intenurs: Toko Pharmaceutical Ind. Co., Ltd., Tokyo; and Catlep: Sumitomo Pharmaceuticals Co., Ltd., Osaka) were used. As TDS, three products containing nitroglycerin (GTN—Millisrol Tape: Nippon Kayaku Co., Ltd., Tokyo; Nitroderm Patch: Ciba-Geigy, Japan, Ltd., Hyogo; and Minitro Tape: Nisshin Flour Milling Co., Ltd., Tokyo) and those containing isosorbide dinitrate (ISDN—Frandol-S Tape: Toa Eiyo Co., Ltd., Tokyo; Rifatac Tape: Meiji Seika Kaisha, Ltd., Tokyo; and Isopit Tape: Toko Pharmaceutical Ind. Co., Ltd). were selected.

Release Study

JP XII Apparatus 2 was employed for the release study (2).

1. Watch glass method (WG): According to Shah et al. (5), an aluminum plaster shell loaded with a semisolid formulation (ca. 0.4 g) was held between a watch glass (50 mm diameter) and a stainless steel window screen (18 mesh) by a three clips (Fig. 1). Effective release area was 4.6 cm^2.
2. Rotating dialysis cell method (RDC): A PTSW-type dissolution apparatus was used in accordance with Dibbern and Wirbitzki (7). A semisolid formulation (ca. 0.5g) was applied to a cell holder and the holder was covered by a sheet of hydrophilic membrane filter (Durapore HVLP type, pore size 0.45 μm, Millipore Corp., Bedford, MA, USA). Three milliliters of 1/15 M phosphate buffer (pH 7.4) was added to the cell holder (Fig. 2).
3. Disk assembly method (DA): A DA diffusion cell by Botari et al. (8), with a slight modification, has a semisolid formulation loading part made of acrylic plate with 1 mm depth and 20 mm in diameter (Fig. 3a). About 0.3g of a semi-solid formulation was ap-

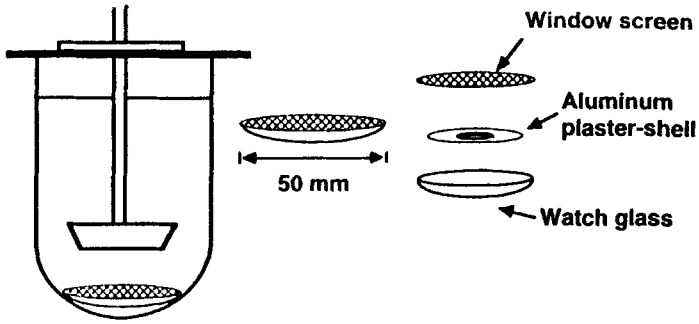

Figure 1. Schematic illustration of watch glass method.

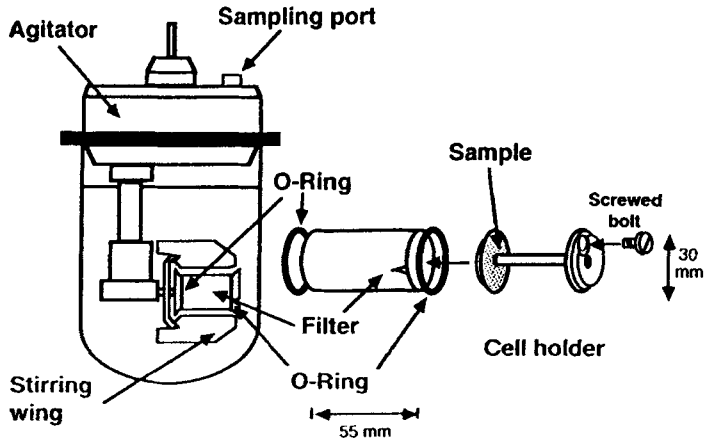

Figure 2. Schematic illustration of rotating dialysis cell method.

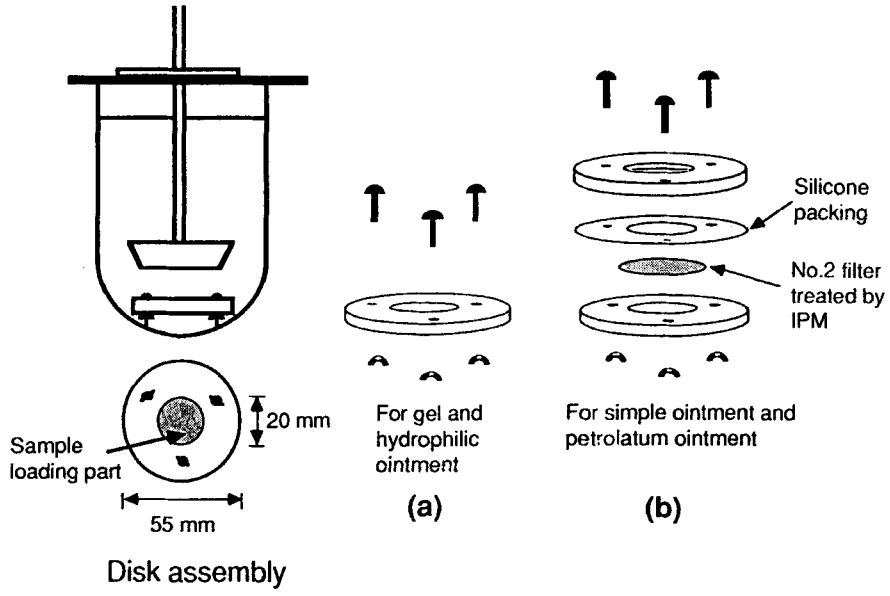

Figure 3. Schematic illustration of disk assembly method.

plied. A sheet of qualitative filter paper (No. 2, Toyo Roshi Kaisha, Ltd., Tokyo) was dipped in isopropyl myristate (IPM—Tokyo Kasei Kogyo Co., Tokyo) and excess IPM was wiped away by Kimwipes® (6). This IPM-saturated filter paper was applied to a surface covered with simple ointment and petrolatum ointment. A silicone packing and disk plate were put on the rim of the acrylic plate, and the resulting sample plate was held with screws (Fig. 3b). Effective release rate was 3.14 cm^2.

Dissolution medium was 1/15 M phosphate buffer (pH 7.4) for the semisolid formulations containing IDM. Paddle rotating speed was set at 100 rpm, but at 50 rpm for gel alone.

For cataplasms, the same disk assembly was used, but an IPM-saturated hydrophobic membrane filter (Durapore HVHP type, pore size 0.45 μm, Millipore Corp.) was applied to the release surface (Fig. 4). Dissolution medium was the same as above, and paddle speed was set at 100 rpm.

Patch and tape formulations were evaluated by fitting assemblies to individual product sizes and two-sided adhesive tape. Figure 5 illustrates cases of small and large patch and tape formulations: For small sizes, a

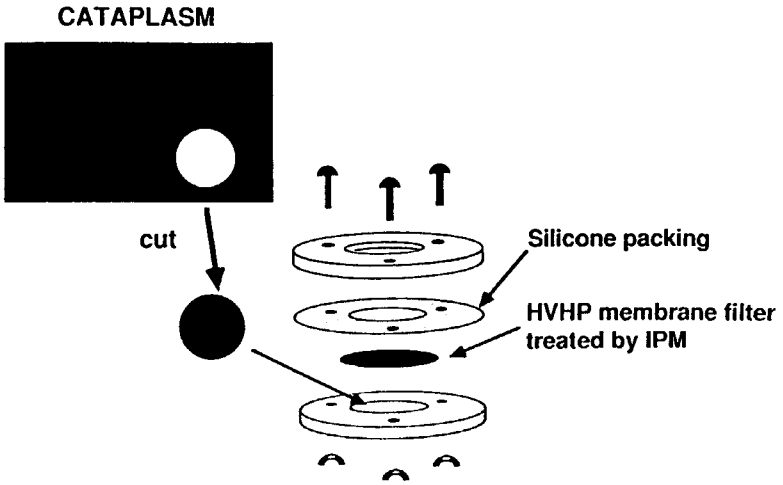

Figure 4. Schematic illustration of disk assembly for cataplasm method.

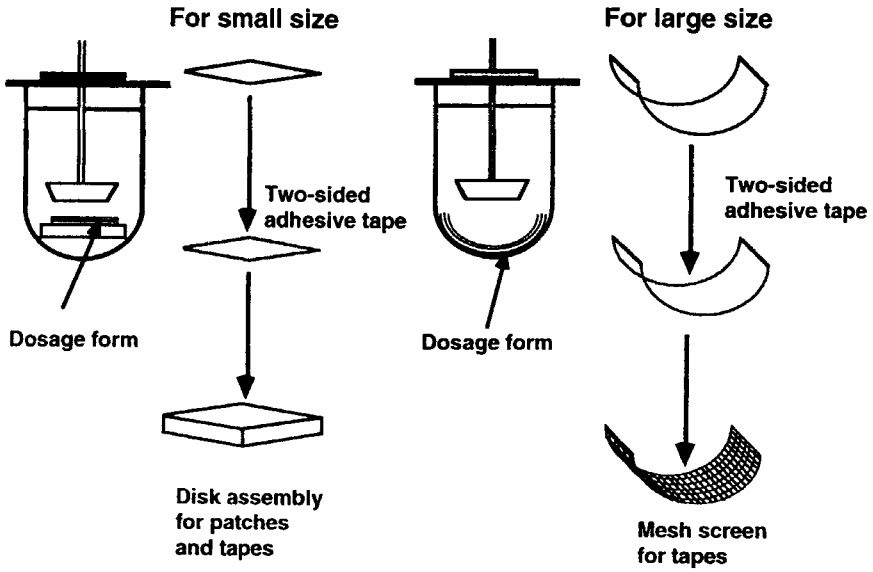

Figure 5. Schematic illustration of modified disk assembly method.

disk assembly similar to that for semisolid formulations was used, whereas for large sizes, mesh screen was used and fitted with dosage form to the concave shape of the bottle. Distilled water was used as dissolution medium and rotation was 50 rpm.

Dissolution medium was kept at 32 ± 0.5°C for all methods. At predetermined intervals a 5 ml sample was withdrawn to measure the amount of drug release. The same amount of fresh medium was added to keep the volume constant throughout the experiment.

Analytical Methods

IDM was determined by an ultraviolet (UV) detector at 265 nm. GTN and ISDN were determined by high-performance liquid chromatography (HPLC) according to Shah et al. (9) and Hatanaka et al. (10), respectively.

RESULTS AND DISCUSSION

Figure 6 shows release profiles of IDM from four semisolid formulations using the three methods (WG, RDC, and DA). These methods showed the same rank order of IDM release from each vehicle (gel > hydrophilic ointment > simple ointment > petrolatum ointment). To evaluate reproducibility of the methods, relative standard deviations (*SD*/mean) were calculated. These are plotted in Fig. 7. DA had the minimum variance in the release amount and rate except for simple ointment. Table 1 summarizes comparisons of the three methods for a quality test. RDC and DA were easy to use in synthetic membrane, whereas WG is not; WG and DA had better handling and reproducibility than RDC. All methods can be automatically implemented. It was concluded from these findings that DA was the best method among the three, and it was further investigated.

Figure 8 shows release profiles of IDM from gel and hydrophilic ointments containing 0.7%, 1.0%, and 1.3% of the drug. Since IDM was released so rapidly from gel (Fig. 6), rotation speed of the paddle was decreased from 100 to 50 rpm; the exact release rate (amount) was then easy to determine. It is clear from Fig. 8 that the different concentrations of IDM in vehicles reflected different release profiles. Figure 8 also shows release profiles of IDM from simple ointments and petrolatum ointments. In contrast to gel, release rates from these lipophilic vehicles were very low (Fig. 6), this was due to poor affinity of the vehicles to the test medium. IPM-saturated synthetic membrane was then applied to increase the drug release from simple ointment and petrolatum ointment (11). When using the membrane with IPM, the initial amount of the drug in the lipophilic vehicles reflected the release pattern as true in cases of gel and hydrophilic ointment (Fig. 9).

A storage test was made on the hydrophilic ointment as a representative of the four semisolid formulations over a period of 4 weeks at 60°C (Fig. 10). The drug release rate decreased with storage of the sample. The release rate after 4 weeks of storage was about half that with no storage, probably due to viscosity change of the vehicle. Increased hardness in a vehicle contributes to a decrease in diffusivity or release rate of a drug. The release behavior from a formulation can be used to determine viscosity change of the vehicle.

In addition to these semisolid vehicles, cataplasms widely used in Japan were assessed. The vehicles were greatly swollen in an aqueous dissolution medium because they contain gel-formed hydrophilic polymers. To

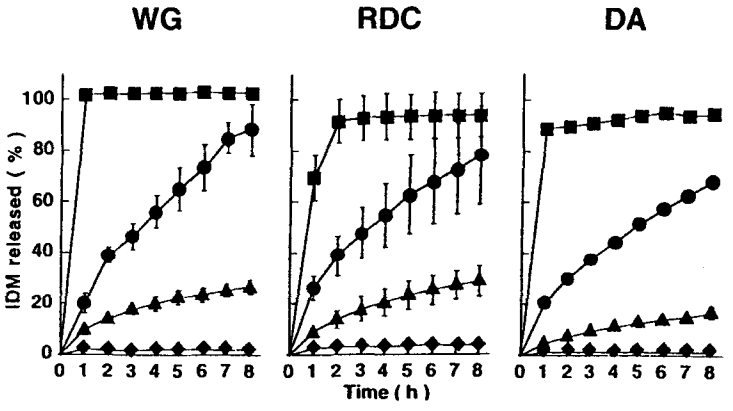

Figure 6. Release profiles of IDM from various ointments containing 1% IDM using different methods. ■, gel; ●, hydrophilic ointment; ▲, simple ointment; ◆, petrolatum ointment. Each value represents the mean ± *SD* (n = 3).

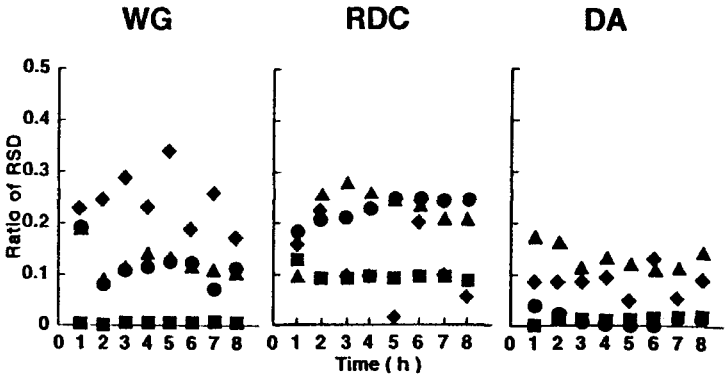

Figure 7. Relative standard deviation (RSD) of release profiles in Fig. 6. Symbols the same as in Fig. 6.

Table 1

Comparison of the Three Methods of Dissolution Testing

Criterion	WG	RDC	DA
Application to membrane	Difficult	Available	Available
Handling	Easy	Complicated	Easy
Reproducibility	Good	Poor	Very good
Adaptation to automated sampling	Easy	Easy	Easy

suppress the swelling, hydrophilic or hydrophobic membrane filter with and without IPM was applied to the cataplasms and the effect was evaluated. No or little suppression effect was observed for hydrophilic membrane even with IPM; nor was any IDM release found by hydrophobic membrane without IPM. When a sheet of IPM-saturated hydrophobic membrane filter was applied to the surface of the vehicles, the swelling was suppressed, a constant surface area was retained on the dissolution medium, and adequate IDM release was observed.

Figure 11 shows the time course of cumulative amount of IDM release from commercial cataplasms A and B. These products were studied for their storage stability over the same period as the hydrophilic ointment. The release profile of product A was the same as

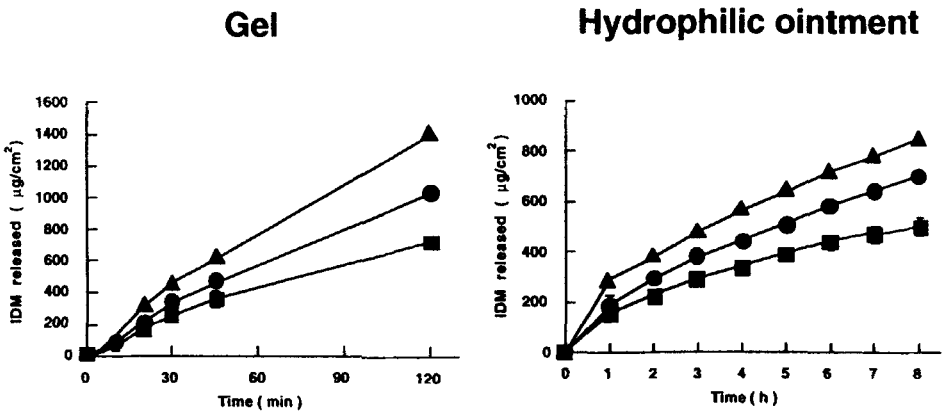

Figure 8. Release profiles of IDM from various ointments containing different concentrations of IDM using the DA method. ■, 0.7% IDM; ●, 1.0% IDM; ▲, 1.3% IDM. Each value represents the mean ± *SD* (n = 3). *SD* was almost contained in each symbol.

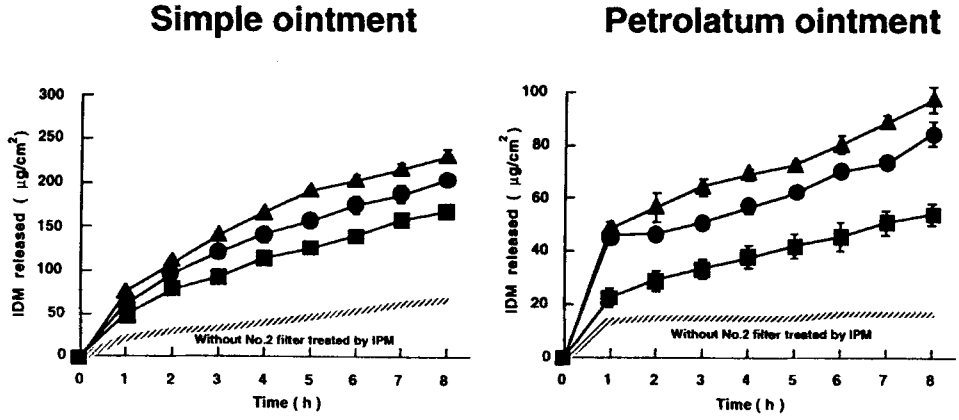

Figure 9. Release profiles of IDM from various ointments containing different concentrations of IDM using the DA method with a No. 2 filter treated by IPM. ■, 0.7% IDM; ●, 1.0% IDM; ▲, 1.3% IDM. Each value represents the mean ± *SD* (n = 3). *SD* was almost contained in each symbol.

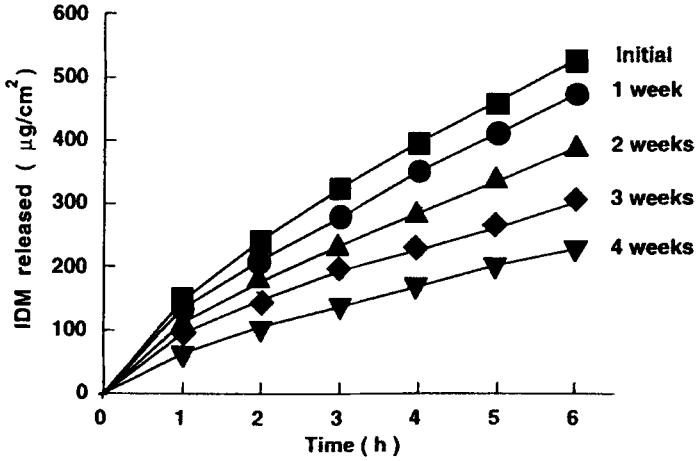

Figure 10. Release profiles of IDM from various ointments containing 1% IDM before and after being stored for 4 weeks at 60°C using the DA method. Each value represents the mean ± *SD* (n = 3). *SD* was almost contained in each symbol.

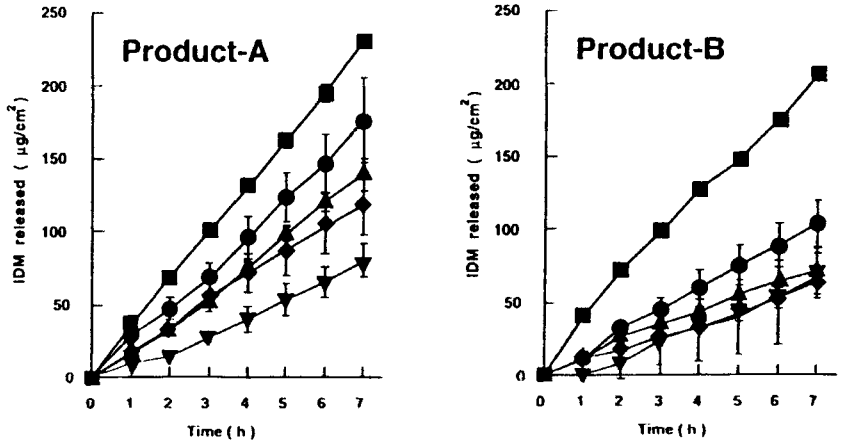

Figure 11. Release profiles of IDM from product A and product B containing 0.5% IDM using the DA method with HVHP membrane filter treated by IPM. ■, initial; ●, 60°C-1W; ▲, 60°C-2W; ◆, 60°C-3W; ▼, 60°C-4W. Each value represents the mean ± *SD* (n = 3).

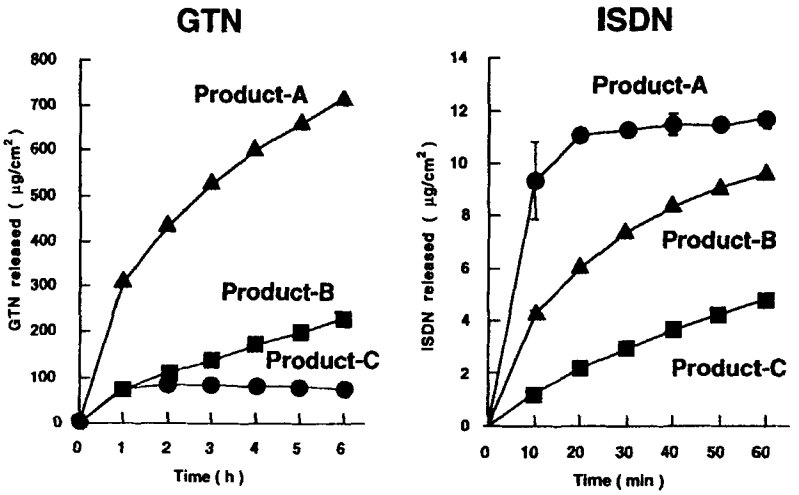

Figure 12. A comparison of the release profiles of GTN and ISDN from product A, product B, and product C using the DA method. Each value represents the mean ± *SD* (n = 3).

that of B at under the initial conditions, but the rate of release A became higher than B with the passage of time. DA can thus be used to assess quality decrease of cataplasms due to their storage.

Finally, drug release studies were conducted on the three GTN TDSs (one patch and two tapes) and three ISDN tapes which are marketed in Japan. These products have different sizes and forms; some of them cannot be applied to the assembly of DA. Patch and tape formulations therefore were evaluated by fitting the assembly to individual product size (Fig. 5). Figure 12 shows the release profiles of GTN and ISDN from each product. Great differences in release amount and rates were observed among the products, except probably for GTN product A, which has a release-limiting membrane. Release kinetics parameters such as T_{75} (time to show 75% release) and D_{60} (percent release over 60 min) for quality control can be calculated from these results. They do not, however, predict the in vivo absorption rates: these products may show the same clinical efficacy because the stratum corneum exists as a barrier to the percutaneous absorption of a drug (12).

CONCLUSION

DA can be viewed as the most popular "official" dissolution method. Synthetic membranes were applied to improve the release characteristics for some vehicles. They provide a possible means of estimating the difference in drug content and storage changes in topical formulations from drug release profiles of ointments. DA is a useful tool for a quantitative release test aimed at quality control of topical formulations; it can be used to check lot-to-lot uniformity and in a stability test. Minor modification of the assembly, however, is necessary for patches and tapes because of their different forms and sizes.

Various topical formulation products will be developed in the future. A standard or official assessment method for all topical formulations is required immediately.

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