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Stability and Evaluation of Sustained-release Isosorbide Dinitrate Preparations

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The characteristics such as weight variations, hardness, drug content, release properties and the conservation stability of three commercial sustained-release formulations (Nitrol-R®, NTR; Frandol®, FRD; Nitrol®, NT) of isosorbide dinitrate were determined. NTR and FRD showed the sustained-release properties with the release rate of NTR being higher than that of FRD. These preparations were maintained under five conditions that are based on the composite experimental design composing the temperature and the humidity. NTR was softened by humidity to a greater extent than FRD. The weight of NTR tended to increase under proportion to the humidity. The hardness of FRD was increased in the conditions of high temperature and low humidity. This phenomenon can be explained by the fact that the melted wax in the tablet penetrated the gaps and hardened after cooling.

The contents of NTR remained constant against the rise in temperature and humidity; it was assumed that the capsule worked to protect the inner granules. During the 14-day stability test, the residual rate of isosorbide dinitrate was predicted by multiple regression analysis and the results are illustrated three-dimensionally. The predicted residual rate of isosorbide dinitrate on NTR and FRD agreed well with the experimental data. The release profiles of these sustained-release preparations were influenced by both temperature and humidity. Guaranteed quality and efficacy of the preparations by hospital pharmacists is required for proper medical treatment.

Key words — controlled release preparations, isosorbide dinitrate, Nitrol-R, Frandol, characteristics, stability, composite experimental design, multiple regression analysis

Introduction

Recently, to improve patient compliance, many kinds of oral controlled release preparations have been developed¹⁾. Various dosages of oral controlled release preparations have been used clinically in the form of capsules, tablets and granules. Even if each preparation contains the same constituents, the drug release characteristics such as stability and absorption will differ with the dosage form design²⁾. During transport and prescription, the characteristics of various preparations have to be kept by the pharmacist. Isosorbide dinitrate has been used clinically for many years³⁾, but little has been reported about its stability on circulation.

In this study, isosorbide dinitrate preparations were used as a model of a sustained-release preparation and were studied on their pharmaceutical characteristics.

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Experimental

1. Materials

Isosorbide dinitrate (Lot. 81040301) was offered from Eisai Co., Ltd. As models of sustained-release preparations of isosorbide dinitrate, Nitrol-R® (NTR, Eisai Co., Ltd.) and Frandol® (FRD, Toa Eiyo Co., Ltd.) were employed. Nitrol® (NT, Eisai Co., Ltd.) was used as a control preparation.

2. Weight variation test

For each preparation, twenty samples were weighed using an AE-balance (Mettler-Toledo Co., Ltd.). The weights of NTR and the granules from the capsule were also measured.

3. Hardness test

A tablet hardness meter (Kitani type) was used to measure the hardness of NT and FRD. Five preparations were selected and measured, and the mean value was taken as the hardness.

4. Content of isosorbide dinitrate

After the preparation was powdered with a mortar and a pestle, the isosorbide dinitrate was extracted with methanol. The isosorbide dinitrate content was then determined by high-performance liquid chromatography (HPLC) using an LC-3 A (Shimadzu Co., Ltd.), equipped a Bondapak C18 Column (Waters Co., Ltd.) set at 220 nm, with a solvent system of acetonitrile and water (55 : 45, v/v). The content of isosorbide dinitrate in 3 samples was determined from the calibration curve which was made in a preliminary experiment.

5. Release test

The test was performed according to the rotating basket method as described in the Pharmacopoeia of Japan XII. As a test fluid, 900 ml ($37 \pm 0.5^\circ\text{C}$) of First Fluid (pH 1.2, up to 2 h) and Second Fluid (pH 6.8, after 2 h) for the disintegration test (Pharmacopoeia of Japan XII) were used. The release test was done at a basket rotation speed of 100 rpm. After the test fluid (5 ml) was withdrawn, the same volume of test fluid was replenished at an appropriate time interval. The amount of released isosorbide dinitrate was assayed by HPLC at 220 nm, and the amounts of isosorbide dinitrate in the samples were determined from the calibration curve which was made in advance.

6. Conservation stability test

The preparations were kept in store box (Nagano Co., Ltd.) for 14 days which was designed to control the temperature and humidity. The preparations were stored according to the composite experimental design^{4,5)} (Fig.

Fig. 1. Composite Experimental Design and Physical Units

1). Preparations were withdrawn at an appropriate time interval, and the weight and the hardness were measured. The content of isosorbide dinitrate after a conservation onset of 14 days was measured again in accordance with the above-mentioned method. As a control, values before the conservation test onset were measured in advance. Three samples were set in each condition, and the mean value was used for evaluation.

Results and Discussion

1. Characteristics

The results of the weight variation test, the hardness test and the content uniformity are shown in **Table 1**. There is no significant difference among the preparation lots. Therefore, we judged that examining only one lot sample produced satisfactory results.

Table 1. Characteristics of Isosorbide Dinitrate Preparations

Preparation Lot.	Weight (g)	Hardness (kg)	Content	
			(mg)	(%)**
Nitrol-R® 1614	0.2069±0.0033*	-	20.63±0.61	103.4
1806	0.2061±0.0035	-	20.27±0.45	101.4
FrandoI® AU339	0.1898±0.0034	4.62±0.42	20.23±0.79	101.1
AL359	0.1905±0.0022	4.31±0.41	20.09±0.78	100.5
Nitrol® 1803	0.1005±0.0005	5.11±0.27	4.87±0.13	97.4
1804	0.0992±0.0006	4.75±0.30	4.87±0.13	97.4

*: mean±S.D.

**: content rate made the value of the indication 100%

2. Release test

The result of the release test of each preparation is shown in **Fig. 2**. NT released 96% of isosorbide dinitrate after 30 minutes, whereas NTR and FRD showed sustained-release characteristics. The percentages of NTR and FRD released after 24 hours were about 99% and 93%, respectively, and the release parameters⁶⁾ of NTR and FRD are shown in **Table 2**. The 16% release time (T16%) of FRD was about two times that of NTR suggesting that the release of isosorbide dinitrate from FRD tends to be slower than that of NTR due to differences in the formulation. The dissolution behaviors of NTR and FRD showed time-dependent and pH-independent properties. These results are consistent with the report of Mizuno et al.⁷⁾.

3. Conservation stability

1) Hardness

The time courses of the change in hardness in FRD and NT are shown in **Fig. 3**. After preservation was started, the hardness after 14 days was often influenced by the humidity, showing a tendency to decrease over time. These results suggest that FRD and NT have to be kept dry.

Fig. 2. Release Profiles of Nitrol-R®(NTR), Frandol®(FRD) and Nitrol®(NT)
 $\triangle$: NTR, $\circ$: FRD, $\square$: NT
 Each point represents the mean $\pm$ S.D. of three examinations

Table 2. Release Parameters of Isosorbide Dinitrate Preparations

	T16%	T50%	T84%	AD(T)	MDT
	(h)	(h)	(h)	(mg·h/ml)	(h)
Nitrol-R®	0.92	2.23	5.39	98.3	3.41
Frandol®	1.10	4.09	15.16	90.8	5.57

T16%; 16% release time, T50%; 50% release time,
 T86%; 84% release time,
 AD(T); area under the dissolution (release) curve,
 MDT; amount dissolved (released) at infinite time

Fig. 3. Time Courses of the Rate of the Hardness in Nitrol® and Frandol®
 $\circ$: 20°C/40%, $\triangle$: 20°C/90%, $\square$: 80°C/40%, $\bullet$: 80°C/90%, $\blacktriangle$: 50°C/65%

2) Weight variation

The time courses of the change in weight in each preparation are shown in Fig. 4. The weight of NTR increased with the humidity, and this seemed to be caused by absorption of water by the capsule. NT and FRD, however did not show significant changes in weight.

Fig. 4. Time Courses of the Rate of Weight in Nitrol-R®, Frandol® and Nitrol®

3) Content of isosorbide dinitrate

The content of isosorbide dinitrate in each preparation decreased with increasing temperature (Fig. 5). Except for the condition at 80°C and at 90% humidity (80°C/90%), little change was observed in the content of NTR.

Fig. 5. Time Courses of the Residual Rate of Isosorbide Dinitrate in Nitrol-R® and Frandol® and Nitrol®

The residual rate of the isosorbide dinitrate (Y) as an objective function of NTR and FRD after 14 days of preservation were predicted by multiple regression analysis with the temperature (X1) and humidity (X2) as independent variables. Prediction equations which were obtained from the multiple regression analysis were

illustrated three-dimensionally (Fig. 6). Regarding the stability of isosorbide dinitrate, FRD was influenced by temperature(X_1) strongly and NTR was influenced by both temperature(X_1) and humidity(X_2). The correlation coefficients of both FRD and NTR were over 0.99. When FRD and NTR were kept under the condition of 80°C/40% for 14 days, the residual rates of isosorbide dinitrate were $3.3 \pm 0.5\%$ (mean $\pm$ S.D., $n = 3$) and $93.0 \pm 10.3\%$, respectively, whereas the predicted residual rates of FRD and NTR were 1.4% and 82.9%. Therefore, it was suggested that the stability of isosorbide dinitrate in these preparations could be predicted from the storage temperature and humidity.

Fig. 6. Three Dimensional Plots of the Residual Rate of Isosorbide Dinitrate in Nitrol-R® and Frاندول® at 14 Days after Preservation

Y : the residual rate of isosorbide dinitrate (%)

X1 : the temperature

X2 : the humidity

4) Release profiles

Fourteen days after the preservation was started, the release test was performed in each preparation, and the results are shown in Fig. 7. FRD was influenced by temperature to a greater extent than NTR. The release parameters of NTR and FRD stored in different conditions are shown in Table 3. The minimum values of the area under the dissolution-time curve for 8 hours (ADT) of FRD at 80°C/40% and 80°C/90% were decreased to 1.5% and 5.4%, respectively, compared to that of the control, but the ADT of NTR at 80°C/40% was reduced to about 60%.

The release rate of NTR tended to be faster than that of FRD. Regarding the conservation stability, moisture absorption occurred in capsules (NTR). In spite of the change in the outward appearance, the content of NTR was maintained better than that of FRD against increasing temperature and humidity. Furthermore, when one capsule of NTR and inner granules was kept for 14 days in the condition of 50°C/55%, the content of isosorbide dinitrate was $17.32 \pm 0.26\text{mg}$ (mean $\pm$ S.D.) and $18.82 \pm 0.86\text{mg}$, respectively. These results indicate that the capsule protected the inner granules against moisture.

Fig. 7 Drug Release Profiles of Nitrol-R® and Frandol® after 14 Days of Preservation
 ○ : 20°C/40%, △ : 20°C/90%, □ : 80°C/40%, ● : 80°C/90%,
 ▲ : 50°C/65%

Table 3 . Release Parameters of Isosorbide Dinitrate Preparations on Storage Conditions

	T16%	T50%	T84%	AD(T)	MDT
	(h)	(h)	(h)	(mg·h/ml)	(h)
Nitrol-R® C	0.92	2.23	5.39	98.33	3.41
I	0.90	2.34	6.06	104.98	3.77
II	0.84	2.81	9.33	89.66	3.82
III	0.71	8.52	101.17	59.80	4.42
IV	1.30×10^{11}	5.88×10^{17}	2.66×10^{24}	0.63	2.09
V	1.07	3.36	10.56	94.53	4.30
Frاندول® C	1.10	4.09	15.16	90.76	5.57
I	1.32	5.50	22.97	86.19	5.89
II	0.97	4.07	17.16	89.00	5.65
III	7.02×10^5	7.71×10^9	8.45×10^{13}	1.37	1.00
IV	9.97×10^5	1.86×10^{14}	3.49×10^{22}	4.94	1.09
V	1.54	6.30	25.78	73.74	5.10

C; control, a value in the experimental on set,

I; 20°- 40%, II; 20°-90%, III; 80°-40%, IV; 80°-90%, V; 50°-65%

FRD, however, which was designed as a wax matrix type preparation, hardened at high temperatures and under dryness but softened with humidification. When FRD was maintained at a high temperature, the melted wax in the tablet must have penetrated the gaps and become hard after cooling.

Sustained release preparations must be recognizable as such by pharماسists, treated and handled according to the dosage form, The care and handling of medical supplies is important to assure the quality until a patient

takes the medicine. The character of the preparation changes with the storage conditions of the medical supplies. The guarantee of drug quality by hospital pharmacists is required for proper medical treatment.

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