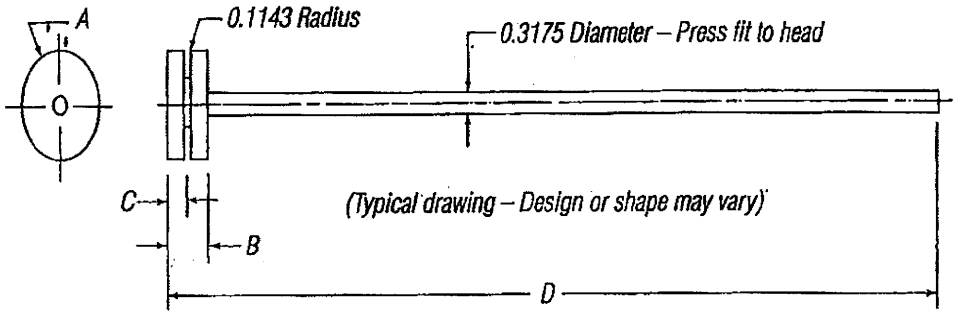


Dimensions are in centimeters

	HEAD				ROD		O-RING
System[a]	*A (Diameter)*	*B*	*C*	Material[b]	*D*	Material[c]	*(not shown)*
1.6cm^2	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5cm^2	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5cm^2	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7cm^2	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10cm^2	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT=Either stainless steel or virgin Teflon.
[c] SS/P=Either stainless steel or Plexiglas.

Fig. 3. Reciprocating Disk Sample Holder.[7]

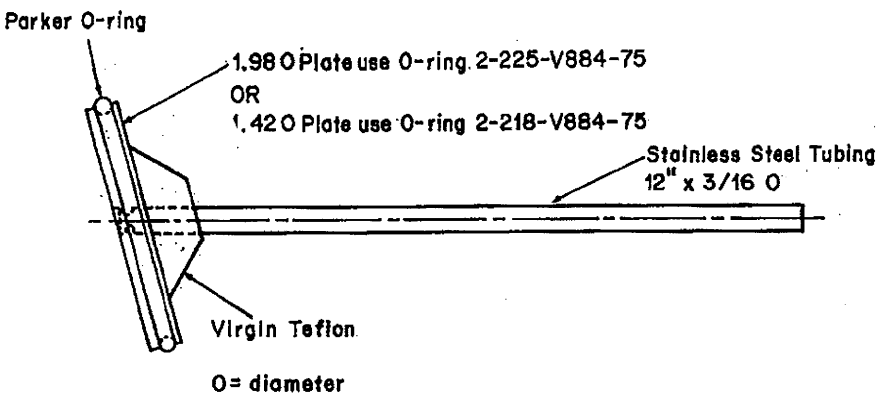


Fig. 4a. Transdermal System Holder—Angled Disk.

cal-shaped sample holder. Trim the excess substrate with a sharp blade.

Sample Preparation C (Other drug delivery systems)—Attach each system to be tested to a suitable holder as described in the individual monograph.

Procedure—Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to temperature, T. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (i.e., water in most cases) to correct for evaporative losses. Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 2* under *Dissolution* ⟨711⟩ for coated tablet drug delivery systems, to *Acceptance Table 1* for transdermal drug delivery systems, or as specified in the individ-

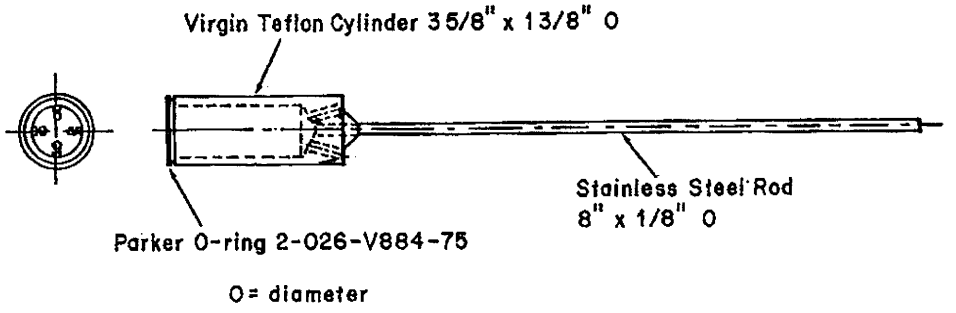


Fig. 4b. Transdermal System Holder—Cylinder.

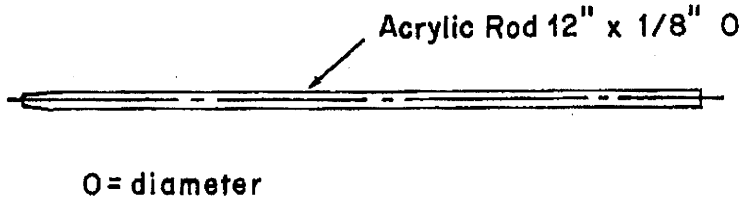
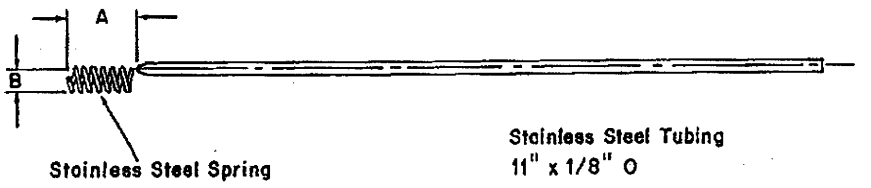


Fig. 4c. Oral Extended-Release Tablet Holder—Rod, Pointed for Gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O= diameter

Fig. 4d. Oral Extended-Release Tablet Holder—Spring Holder.

ual monograph. Continue testing through the three levels unless the results conform at either L_1 or L_2.

⟨726⟩ ELECTROPHORESIS

Electrophoresis refers to the migration of electrically charged proteins, colloids, molecules, or other particles when dissolved or suspended in an electrolyte through which an electric current is passed.

Based upon the type of apparatus used, electrophoretic methods may be divided into two categories, one called *free solution* or moving boundary electrophoresis and the other called *zone electrophoresis*.

In the *free solution* method, a buffered solution of proteins in a U-shaped cell is subjected to an electric current which causes the proteins to form a series of layers in order of decreasing mobility, which are separated by boundaries. Only a part of the fastest moving protein is physically separated from the other proteins, but examination of the moving boundaries using a schlieren optical system provides data for calculation of mobilities and information on the qualitative and quantitative composition of the protein mixture.

In *zone electrophoresis*, the sample is introduced as a narrow zone or spot in a column, slab, or film of buffer. Migration of the components as narrow zones permits their complete separation. Remixing of the separated zones by thermal convection is prevented by stabilizing the electrolyte in a porous matrix such as a powdered solid, or a fibrous material such as paper, or a gel such as starch, agar, or polyacrylamide.

Various methods of zone electrophoresis are widely employed. *Gel electrophoresis*, particularly the variant called *disk electrophoresis*, is especially useful for protein separation because of its high resolving power.

Gel electrophoresis, which is employed by the compendium, is discussed in more detail following the presentation of some theoretical principles and methodological practices, which are shared in varying degrees by all electrophoretic methods.

The electrophoretic migration observed for particles of a particular substance depends on characteristics of the parti-

QUALIFICATION AND VALIDATION

Due to the nature of the test method, quality by design is an important qualification aspect for *in vitro* dissolution test equipment. Any irregularities such as vibration or undesired agitation by mechanical imperfections are to be avoided.

Qualification of the dissolution test equipment has to consider the dimensions and tolerances of the apparatus. Critical test parameters, such as temperature and volume of dissolution medium, rotation speed or liquid flow rate, sampling probes and procedures have to be monitored periodically during the periods of use.

The performance of the dissolution test equipment may be monitored by testing a reference product which is sensitive to hydrodynamic conditions. Such tests may be performed periodically or continuously for comparative reasons with other laboratories.

During testing, critical inspection and observation are required. This approach is especially important to explain any out-lying results.

Validation of automated systems, whether concerning the sampling and analytical part or the dissolution media preparation and test performance, has to consider accuracy, precision, and the avoidance of contamination by any dilutions, transfers, cleaning and sample or solvent preparation procedures.

DISSOLUTION SPECIFICATIONS FOR ORAL DOSAGE FORMS

The dissolution specification is expressed as the quantity *Q* of the active substance as a percentage of the content stated on the product label, which is dissolved in a specified time frame.

Conventional-release dosage forms

Unless otherwise specified, the value of *Q* is 75 per cent. In most cases, when tested under reasonable and justified test conditions at least 75 per cent of the active substance is released within 45 min. Typically, one limit is specified to ensure that most of the active substance is dissolved within the pre-set time period.

In cases where a longer release time than that recommended above is justified, limits at 2 time intervals may be specified.

Prolonged-release dosage forms

A manufacturer's dissolution specification for prolonged-release dosage forms is normally expected to consist of 3 or more points. The first specification point is intended to prevent unintended rapid release of the active substance ('dose dumping'). It is therefore set after a testing period corresponding to a dissolved amount of typically 20 per cent to 30 per cent. The second specification point defines the dissolution pattern and so is set at around 50 per cent release. The final specification point is intended to ensure almost complete release which is generally understood as more than 80 per cent release.

Delayed-release dosage forms

A delayed-release dosage form may release the active substance(s) fractionally or totally according to the formulation design when tested in different dissolution media, e.g. in increasing pH conditions. Dissolution specifications have, therefore, to be decided from case to case.

Gastro-resistant dosage forms require at least 2 specification points in a sequential test and 2 different specifications in a parallel test. In a sequential test, the first specification point is set after 1 h or 2 h in acidic medium and the second one at a pre-set time period of testing in an adequate buffer solution (preferably pH 6.8). Unless otherwise specified, the value of *Q* is 75 per cent.

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2.9.4. DISSOLUTION TEST FOR TRANSDERMAL PATCHES

This test is used to determine the dissolution rate of the active ingredients of transdermal patches.

1. DISK ASSEMBLY METHOD

Equipment. Use the paddle and vessel assembly from the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*) with the addition of a stainless steel disk assembly (SSDA) in the form of a net with an aperture of 125 µm (see Figure 2.9.4.-1).

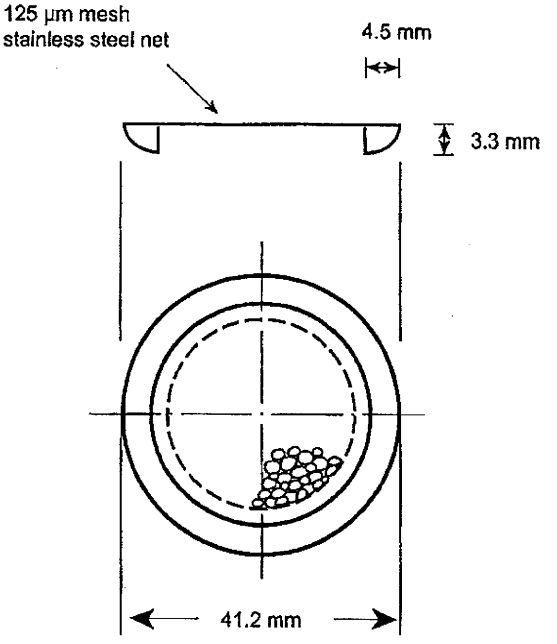


Figure 2.9.4.-1. – *Disk assembly*

The SSDA holds the system at the bottom of the vessel and is designed to minimise any dead volume between the SSDA and the bottom of the vessel. The SSDA holds the patch flat, with the release surface uppermost and parallel to the bottom of the paddle blade. A distance of 25 ± 2 mm between the bottom of the paddle blade and the surface of the SSDA is maintained during the test (see Figure 2.9.4.-2). The temperature is maintained at 32 ± 0.5 °C. The vessel may be covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Apply the patch to the SSDA, ensuring that the release surface of the patch is as flat as possible. The patch may be attached to the SSDA by a prescribed adhesive or by a strip of a double-sided adhesive tape. The adhesive or tape are previously tested for the absence of interference with the assay and of adsorption of the active ingredient(s). Press the patch, release surface facing up, onto the side of the SSDA made adhesive. The applied patch must not overlap the borders of the SSDA. For this purpose and provided that the preparation is homogeneous and uniformly spread on the outer covering, an appropriate and exactly measured piece of the patch

may be cut and used for testing the dissolution rate. This procedure may also be necessary to achieve appropriate sink conditions. This procedure must not be applied to membrane-type patches. Place the patch mounted on the SSDA flat at the bottom of the vessel with the release surface facing upwards. Immediately rotate the paddle at 100 r/min, for example. At predetermined intervals, withdraw a sample from the zone midway between the surface of the dissolution medium and the top of the blade, not less than 1 cm from the vessel wall.

Perform the assay on each sample, correcting for any volume losses, as necessary. Repeat the test with additional patches.

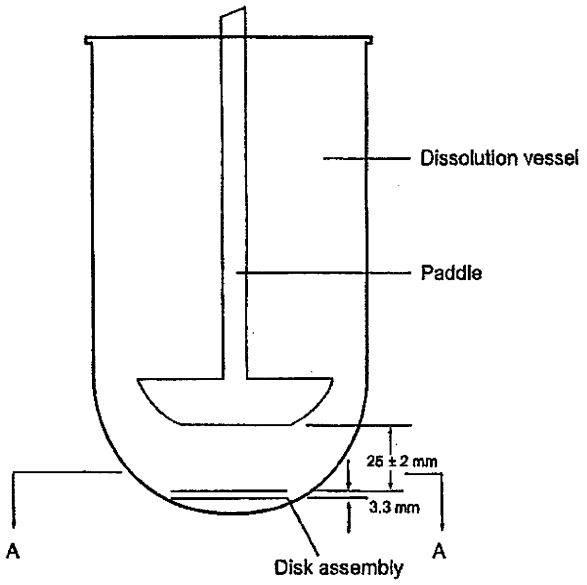


Figure 2.9.4.-2. – *Paddle and disk*

2. CELL METHOD

Equipment. Use the paddle and vessel assembly from the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*) with the addition of the extraction cell (*cell*).

The *cell* is made of chemically inert materials and consists of a *support*, a *cover* and, if necessary, a *membrane* placed on the patch to isolate it from the medium that may modify or adversely affect the physico-chemical properties of the patch (see Figure 2.9.4.-3).

Support. The central part of the support forms a cavity intended to hold the patch. The cavity has a depth of 2.6 mm and a diameter that is appropriate to the size of the patch to be examined. The following diameters can be used: 27 mm, 38 mm, 45 mm, 52 mm, corresponding to volumes of 1.48 ml, 2.94 ml, 4.13 ml, 5.52 ml, respectively.

Cover. The cover has a central opening with a diameter selected according to the size of the patch to be examined. The patch can thus be precisely centred, and its releasing surface limited. The following diameters may be used: 20 mm, 32 mm, 40 mm, 50 mm corresponding to areas of 3.14 cm^2, 8.03 cm^2, 12.56 cm^2, 19.63 cm^2, respectively. The cover is held in place by nuts screwed onto bolts projecting from the support. The cover is sealed to the support by a rubber ring set on the reservoir.

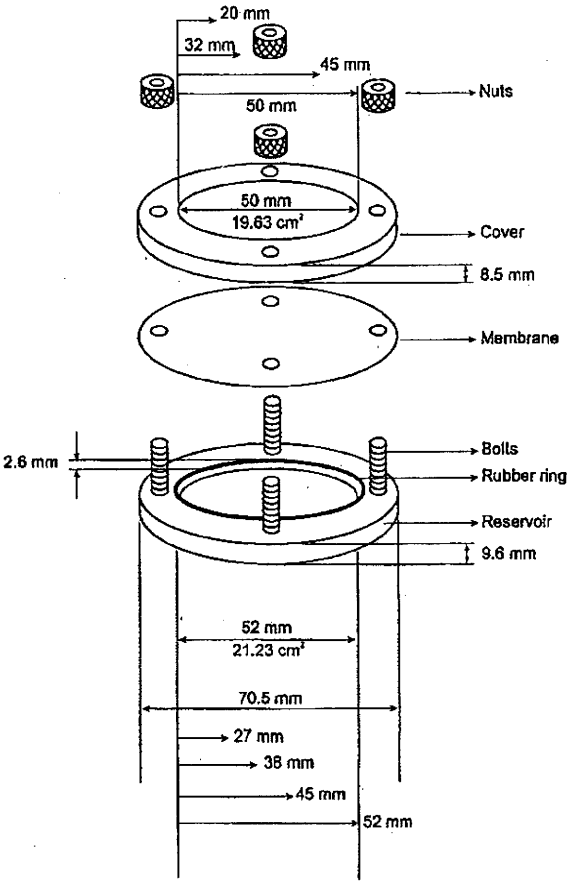


Figure 2.9.4.-3. – *Extraction cell*

Extraction cell. The *cell* holds the patch flat, with the release surface uppermost and parallel to the bottom of the paddle blade. A distance of 25 ± 2 mm is maintained between the paddle blade and the surface of the patch (see Figure 2.9.4.-4). The temperature is maintained at 32 ± 0.5 °C. The vessel may be covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Precisely centre the patch in the *cell* with the releasing surface uppermost. Close the *cell*, if necessary applying a hydrophobic substance (for example, petrolatum) to the flat surfaces to ensure the seal, and ensure that the patch stays in place. Introduce the cell flat into the bottom of the vessel with the cover facing upwards. Immediately rotate the paddle, at 100 r/min for example. At predetermined intervals, withdraw a sample from the zone midway between the surface of the dissolution medium and the top of the paddle blade, not less than 1 cm from the vessel wall.

Perform the assay on each sample, correcting for any volume losses, as necessary. Repeat the test with additional patches.

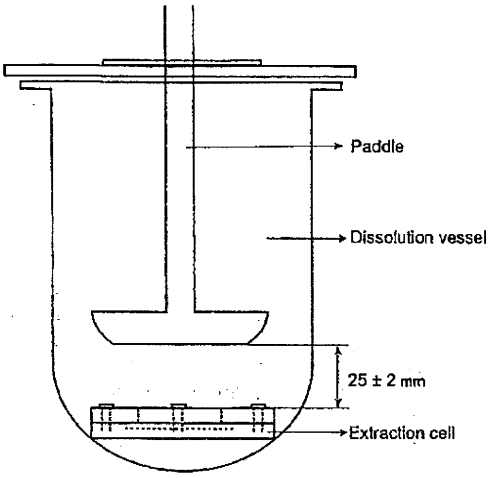


Figure 2.9.4.-4. – *Paddle over extraction cell*

3. ROTATING CYLINDER METHOD

Equipment. Use the assembly of the paddle apparatus described in the dissolution test for solid oral dosage forms (*2.9.3*). Replace the paddle and shaft with a stainless steel cylinder stirring element (*cylinder*) (see Figure 2.9.4.-5). The patch is placed on the *cylinder* at the beginning of each test. The distance between the inside bottom of the vessel and the *cylinder* is maintained at 25 ± 2 mm during the test. The temperature is maintained at 32 ± 0.5 °C. The vessel is covered during the test to minimise evaporation.

Procedure. Place the prescribed volume of the dissolution medium in the vessel and equilibrate the medium to the prescribed temperature. Remove the protective liner from the patch and place the adhesive side on a piece of suitable inert porous membrane that is at least 1 cm larger on all sides than the patch. Place the patch on a clean surface with the membrane in contact with this surface. Two systems for adhesion to the *cylinder* may be used:

- apply a suitable adhesive to the exposed membrane borders and, if necessary, to the back of the patch,
- apply a double-sided adhesive tape to the external wall of the *cylinder*.

Using gentle pressure, carefully apply the non-adhesive side of the patch to the *cylinder*, so that the release surface is in contact with the dissolution medium and the long axis of the patch fits around the circumference of the *cylinder*.

The system for adhesion used is previously tested for absence of interference with the assay and of adsorption of the active ingredient(s).

Place the *cylinder* in the apparatus, and immediately rotate the *cylinder* at 100 r/min, for example. At determined intervals, withdraw a sample of dissolution medium from a zone midway between the surface of the dissolution medium and the top of the rotating *cylinder*, and not less than 1 cm from the vessel wall.

Perform the assay on each sample as directed in the individual monograph, correcting for any volume withdrawn, as necessary. Repeat the test with additional patches.

Interpretation. The requirements are met if the quantity of active ingredient(s) released from the patch, expressed as the amount per surface area per time unit, is within the prescribed limits at the defined sampling times.

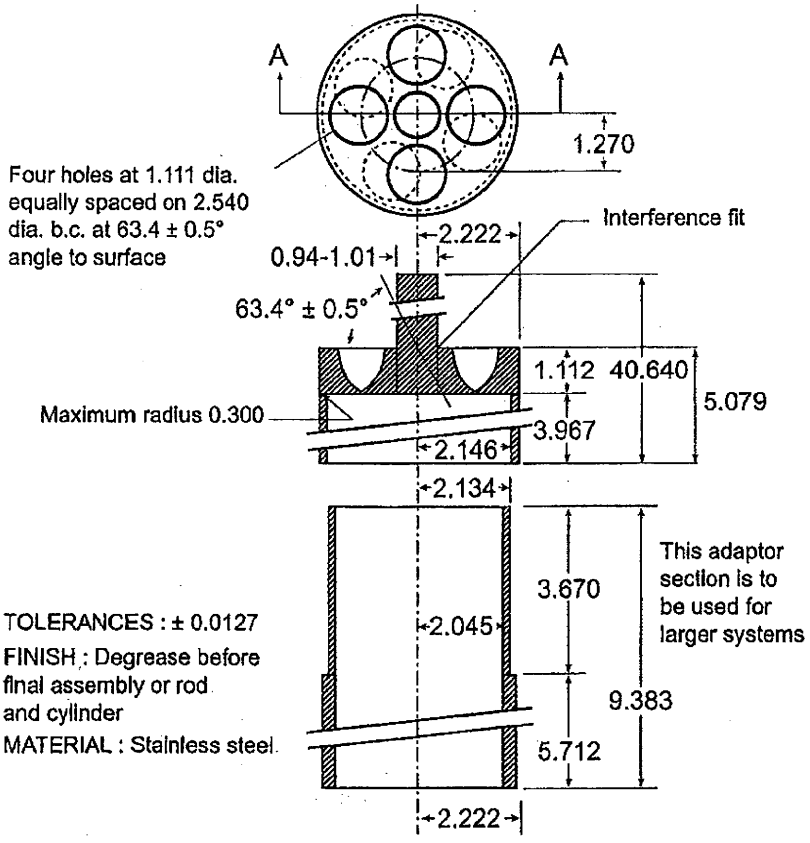


Figure 2.9.4.-5. – *Cylinder stirring element*
Dimensions in centimetres

suitable spectrophotometer, using water as the blank: the ratio A_{245}/A_{262} is between 0.63 and 0.67.

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_6H_6N_2O$ dissolved, employing the procedure set forth in the *Assay for niacin or niacinamide, pyridoxine hydrochloride, riboflavin, and thiamine* under *Water-soluble Vitamins Tablets*, using filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Niacinamide RS in the same medium.

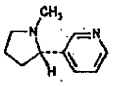
Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_6H_6N_2O$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—Proceed with Tablets as directed for *Chemical Method* under *Niacin or Niacinamide Assay* ⟨441⟩, using *Standard Niacinamide Preparation* as the *Standard Preparation* in the *Assay Procedure:* and the following as the *Assay Preparation.* Weigh and finely powder not less than 10 Tablets. Weigh accurately a quantity of the powder, equivalent to about 25 mg of niacinamide, and transfer with the aid of about 50 mL of water to a 250-mL volumetric flask. Heat, if necessary, until no more dissolves, cool, dilute with water to volume, and mix. Pipet 10 mL of the solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Calculate the quantity, in mg, of $C_6H_6N_2O$ in the portion of Tablets taken by the formula:

$$25(A_U / A_S).$$

Nicotine



$C_{10}H_{14}N_2$　162.23

3-(1-Methyl-2-pyrrolidinyl)pyridine.

β-Pyridyl-α-*N*-methyl pyrrolidine　[*54-11-5*].

» Nicotine contains not less than 99.0 percent and not more than 101.0 percent of $C_{10}H_{14}N_2$, calculated on the anhydrous basis.

Packaging and storage—Store under nitrogen in well-closed containers below 25°, protected from light and moisture.

USP Reference standards ⟨11⟩—

USP Nicotine Bitartrate Dihydrate RS

Identification, *Ultraviolet Absorption* ⟨197U⟩—

Solutions—Prepare a solution of Nicotine in water having a concentration of about 1 mg per mL. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix to obtain the test solution. Transfer an amount of USP Nicotine Bitartrate Dihydrate RS, equivalent to about 50 mg of nicotine, to a 25-mL glass-stoppered tube. Add 5 mL of 6 N ammonium hydroxide; 2 mL of 1 N sodium hydroxide, and 20 mL of *n*-hexane. Shake for 5 minutes, allow the phases to separate, transfer the upper *n*-hexane layer to a vial, and evaporate with a stream of nitrogen gas. [NOTE—Avoid excessive drying to prevent loss of nicotine.] Dissolve the residue of the nicotine so obtained in water to obtain a solution having a concentration of about 1 mg per mL. Dilute 1.0 mL of this solution with 0.1 N hydrochloric acid to 50.0 mL, and mix to obtain the Standard solution.

Specific rotation ⟨781S⟩: between −130° and −143°.

Test solution: 20 mg per mL, in alcohol.

Water, *Method I* ⟨921⟩: not more than 0.5%.

Heavy metals, *Method II* ⟨231⟩: not more than 0.002%.

Chromatographic purity—

Test solution—Dissolve about 0.13 g of Nicotine, accurately weighed, in dichloromethane, dilute with dichloromethane to 25.0 mL, and mix.

Reference solutions—Dilute accurately measured volumes of the *Test solution* quantitatively, and stepwise if necessary, with dichloromethane to obtain *Reference solution A* and *Reference solution B* having concentrations of about 26 µg per mL and 52 µg per mL, respectively.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector maintained at 270° and a 0.53-mm × 30-m fused silica column bonded with a 1.5-µm layer of phase G1. Helium is used as the carrier gas at a flow rate of 20 mL per minute. The column temperature is maintained at 50° for 6 seconds, then programmed to rise from 50° to 250° at 6° per minute, and finally held isothermally at 250° for 3 minutes.

Procedure—Separately inject equal volumes (about 1 µL) of the *Test solution, Reference solution A,* and *Reference solution B* into the chromatograph, and allow the *Test solution* to elute for not less than 2.5 times the retention time of nicotine. Record the chromatograms, and measure all of the peak responses. The sum of the peak responses, excluding that of nicotine, from the *Test solution* is not more than that of the nicotine response from *Reference solution B* (1.0%), and no single peak response is greater than that of the nicotine response from *Reference solution A* (0.5%).

Assay—Dissolve about 60 mg of Nicotine, accurately weighed, in 40 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 8.11 mg of $C_{10}H_{14}N_2$.

ニコチン経皮吸収型製剤

Nicotine Transdermal System

» Nicotine Transdermal System contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nicotine ($C_{10}H_{14}N_2$).

Packaging and storage—Preserve in the hermetic, light-resistant, unit-dose pouch.

Labeling—The labeling indicates the *Drug Release Test* with which the product complies.

USP Reference standards ⟨11⟩—

USP Nicotine Bitartrate Dihydrate RS

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Drug release ⟨724⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1*.

Medium: Phosphoric acid solution (1 in 1000); 250 mL, in a tall-form beaker.

Apparatus 7—Proceed as directed in the chapter, using the transdermal system holder–cylinder (see *Figure 4b*). Center the Transdermal System onto a dry, unused 10-cm × 10-cm piece of Cuprophan dialysis membrane with the adhesive side against the membrane, taking care to eliminate air bubbles between the membrane and the release surface. Attach the membrane to the cylinder using two Parker O-rings, such that one of the borders of the transdermal system is aligned to the groove and

it is wrapped around the cylinder. The filled beakers are weighed and pre-equilibrated to 32.0 ± 0.3°, prior to immersing the test sample. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of 2.0 ± 0.1 cm. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of *Medium*, weighed and pre-equilibrated to 32.0 ± 0.3°. At the end of each release interval, allow the beakers to cool to room temperature, make up for evaporative losses by adding water to obtain the original weight, and mix. This solution is the final *Test solution*.

Times: 2, 12, and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Transfer 0.2 mL of *N,N*-dimethyloctylamine to a 1-L volumetric flask, add 220 mL of acetonitrile, and mix. Add 300 mL of water, 0.2 mL of glacial acetic acid, 0.20 g of anhydrous sodium acetate, and 0.55 g of sodium 1-dodecanesulfonate, and dilute with water to volume. Mix for 1 hour until clear. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Equilibration of the column may take as long as 3 hours.]

Standard solution—Dissolve an accurately weighed quantity of USP Nicotine Bitartrate Dihydrate RS in *Medium*, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.142 mg of nicotine bitartrate per mL (or 0.046 mg nicotine as free base per mL). [NOTE—About 80 mL of this solution is required in order to prepare the *System suitability solution*.]

System suitability solution—Transfer 8 mg (free base) of nicotine to a 100-mL volumetric flask, and dissolve in 10 mL of acetonitrile. Add 5 mL of 30% hydrogen peroxide, and allow 15 minutes to react. Dilute with *Medium* to volume, and mix. Transfer 20 mL of this solution to a 100-mL volumetric flask, dilute with *Standard solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between nicotine and any degradation peaks is not less than 1.1; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of filtered portions of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified below, conforms to *Acceptance Table 1*.

Time (hours)	Amount dissolved
0–2	between 31% and 87%
2–12	between 62% and 191%
12–24	between 85% and 261%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2*.

Phosphate buffer—Dissolve 40.0 g of sodium chloride, 1.0 g of potassium chloride, 8.66 g of dibasic sodium phosphate, and 1.0 g of monobasic potassium phosphate in 5 L of water.

Medium: *Phosphate buffer;* 500 mL.

Apparatus 6: 50 rpm, double-sided tape being used to attach the Transdermal System to the cylinder.

Times: 6 and 24 hours.

Determine the amount of $C_{10}H_{14}N_2$ released by employing the following method.

Mobile phase—Proceed as directed in the *Assay*.

System suitability solution—Transfer 1.0 mL of the *System suitability solution*, prepared as directed in the *Assay*, to a 100-mL volumetric flask, dilute with *Medium* to volume, and mix.

Standard solution—Pipet 6.0 mL of the *Standard preparation*, prepared as directed in the *Assay*, into a 50-mL volumetric flask, dilute with *Medium* to volume, and mix. Dilute quantitatively and stepwise with *Medium* to obtain an appropriate final concentration.

Test solution—At each of the test times, withdraw a 2-mL aliquot of the solution under test. [NOTE—Replace the aliquots withdrawn for analysis with fresh portions of *Medium*.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 12.5-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution* used for the 6-hour interval, and record the peak responses as directed for *Procedure:* the resolution, *R*, between 4,4′-dipyridyl and nicotine is not less than 5.0; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the filtered portion of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to *Acceptance Table 1*.

Time (hours)	Amount dissolved
6	between 71% and 157%
24	between 156% and 224%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3*.

Medium: water; 900 mL.

Apparatus 5: 50 rpm, the stainless steel disk assembly being replaced with a 5-cm watch glass for an 11-mg Transdermal System and an 8-cm watch glass for a 22-mg Transdermal System.

Times: 1, 2, and 4 hours.

Standard solution—Prepare a solution of USP Nicotine Bitartrate Dihydrate RS in water having a known concentration of nicotine similar to that of the solution under test.

Procedure—Determine the amount of $C_{10}H_{14}N_2$ released by employing UV absorption at the wavelength of maximum absorbance at about 259 nm, in comparison with the *Standard solution*, using water as the blank.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to the following *Acceptance Table*.

Time (hours)	Amount dissolved
1	between 35% and 75%
2	between 55% and 95%
4	not less than 73%

Acceptance Table

Level	Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 5% of the labeled content outside each of the stated ranges; and none is more than 5% of the labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within each of the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 5% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 5% of the labeled content below the stated amount at the final test time; and none of the units is more than 10% of the labeled content outside each of the stated ranges or more than 10% of the labeled content below the stated amount at the final test time.

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 4*.

Medium: 0.025 N hydrochloric acid; 600 mL.

Apparatus 5: 50 rpm, a convex screen being used to hold the Transdermal System in position during testing.

Times: 4 and 16 hours.

Standard solution and *Procedure*—Proceed as directed under *Test 3*.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to *Acceptance Table 1*.

Time (hours)	Amount dissolved
4	between 36% and 66%
16	between 72% and 112%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.

Phosphate buffer, Medium, and *Apparatus*—Proceed as directed under *Test 2*.

Times: 3, 6, and 24 hours.

Mobile phase—Proceed as directed in the *Assay*.

System suitability solution, Standard solution, Test solution, and *Chromatographic system*—Proceed as directed under *Test 2*.

Procedure—Proceed as directed under *Test 2* except to inject about 30 µL.

Tolerances—The amount of $C_{10}H_{14}N_2$ released, as a percentage of the labeled amount of the dose absorbed in vivo, at the times specified, conforms to *Acceptance Table 1*.

Time (hours)	Amount dissolved
3	between 79% and 112%
6	between 108% and 141%
24	between 156% and 202%

Uniformity of dosage units ⟨905⟩: meets the requirements.

Assay—

Mobile phase—Mix 300 mL of acetonitrile, 700 mL of water, and 1 mL of triethylamine, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Nicotine Bitartrate Dihydrate RS in water to obtain a stock solution having a known concentration of about 26.87 mg per mL. Quantitatively dilute a volume of the stock solution with methanol to obtain a solution having a known concentration of about 5.37 mg of USP Nicotine Bitartrate Dihydrate RS per mL. [NOTE—This solution contains 1.75 mg of nicotine per mL.]

System suitability solution—Transfer about 8 mg of 4,4′-dipyridyl to a 25-mL volumetric flask, add 5.0 mL of the *Standard preparation*, dilute with methanol to volume, and mix.

Assay preparation—Cut an accurately counted number of Transdermal Systems, equivalent to about 175 mg of nicotine, based on the label claim, into strips 5 cm^2 in area. Remove the protective liners, if any, from the strips, and discard. Transfer the strips to a 250-mL flask, and add 100.0 mL of methanol. Insert the stopper into the flask, and shake by mechanical means for about 3 hours. Filter, and use the clear filtrate as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 25-cm column containing packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, R, between nicotine and 4,4′-dipyridyl is not less than 5.0. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percent label claim of nicotine ($C_{10}H_{14}N_2$) in each Transdermal System taken by the formula:

$$100(162.23/462.41)(C_S / C_U)(r_U / r_S)$$

in which 162.23 and 462.41 are the molecular weights of nicotine and anhydrous nicotine bitartrate, respectively; C_S is the concentration, in mg per mL, of USP Nicotine Bitartrate Dihydrate RS in the *Standard preparation*; C_U is the nominal concentration of nicotine in the *Assay preparation*, based on the label claim; and r_U and r_S are the nicotine peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

貼付剤，テープ剤の放出試験法

本試験法は，貼付剤，テープ剤等の製剤からの医薬品の放出性を測定する方法である．これらの製剤では，皮膚が大きなバリアーとなるために、必ずしも医薬品の放出性と有効性の関連は明確ではないが、放出性は個々の製剤特性に依存し，製剤ごとの品質管理に有効な試験法である．特に，経皮吸収型製剤の有効成分の放出速度は、適切な管理が必要である．

パドルオーバーディスク法

１．パドルオーバーディスク法の装置（装置４）

装置は、溶出試験法<6.10>のパドル法の装置を用い、パドルとベッセルの他に、試料をベッセルの底に沈めるために、図１に示すステンレス製の 125μm の目開きの網でできたディスク部品を追加して使用する。披験物質を吸着したり、反応したり、分析を妨害しないものであれば、ディスク部品の代わりに、その他の適切な部品を用いてもよい。ディスクは、広げて放出面を上にして貼り付け、パドル翼の底部と平行に設置する。

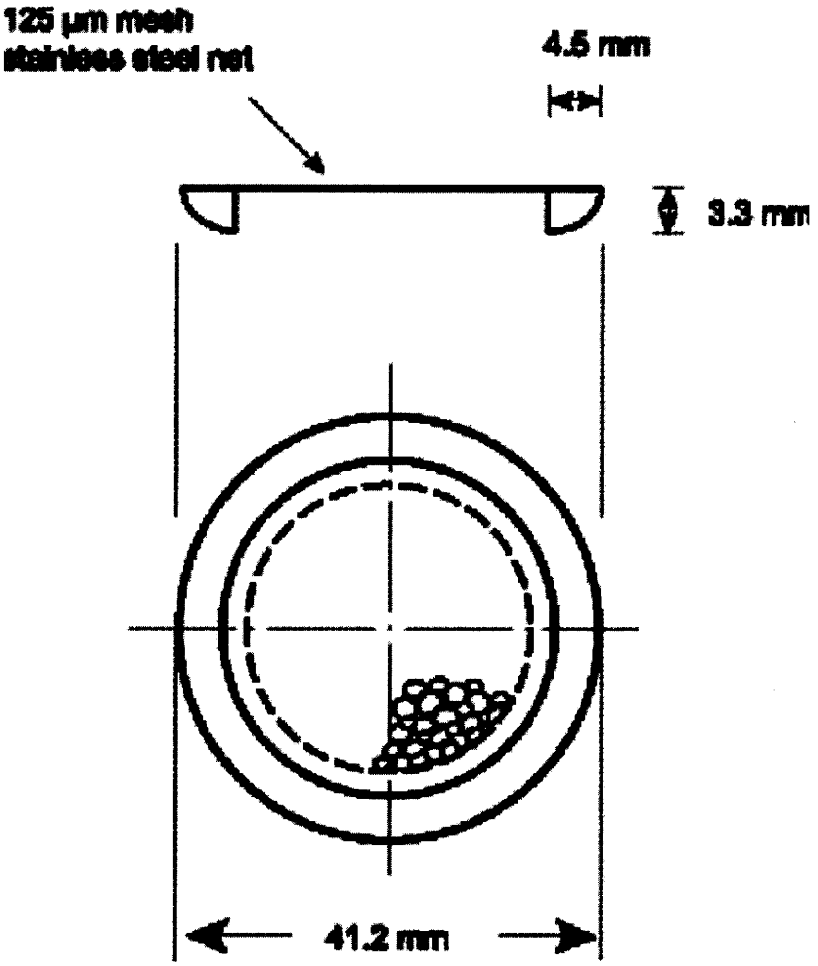


図１　ディスク部品

パドル翼の底部とディスクの表面の距離は、通例、25± 2 mm とし（図２）、試験液の温度は 32 ± 0.5℃° とする。ベッセルはできるだけ試験液の蒸発を防ぐように蓋をする。

その他、装置の適合性や試験液等に関しては、溶出試験法<6.10>の指示に従う。

2．パドルオーバーディスク法の操作

ディスクは入れない状態で、規定された量の試験液をベッセルに入れ、規定の温度にするまで待つ。試験液として、通例、pH5～7の範囲における任意の緩衝液を用いる。また、製剤の形状に影響を与えなければ水－アルコール混液、有機溶媒等を用いることができる。

製剤をできるだけ平らになるように、適切な接着剤で放出面を上になるようにディスクに貼り付ける。製剤は、均一に分布していれば、適切な大きさに、正確に計って切ったものを、放出試験に使用してもかまわない。

必要に応じて、製剤の固定等のために試験液と製剤を隔てる膜を用いることができるが、容易に試験液を通す膜を用い、膜と放出面の間に気泡がはいらないように気をつける。

ディスクを、ベッセルの底部に放出面を上にして、パドル翼の底部や試験液面と平行に設置する。設置後、すみやかにパドルを回し、規定されたサンプリング時間に、パドルの回転翼の上面から試験液面の中間付近で、壁面から1cm以上離れたところから試験液を採取する。

規定された分析法で、溶出した有効成分量を測定する。その也の試料についても同様の操作を行う。

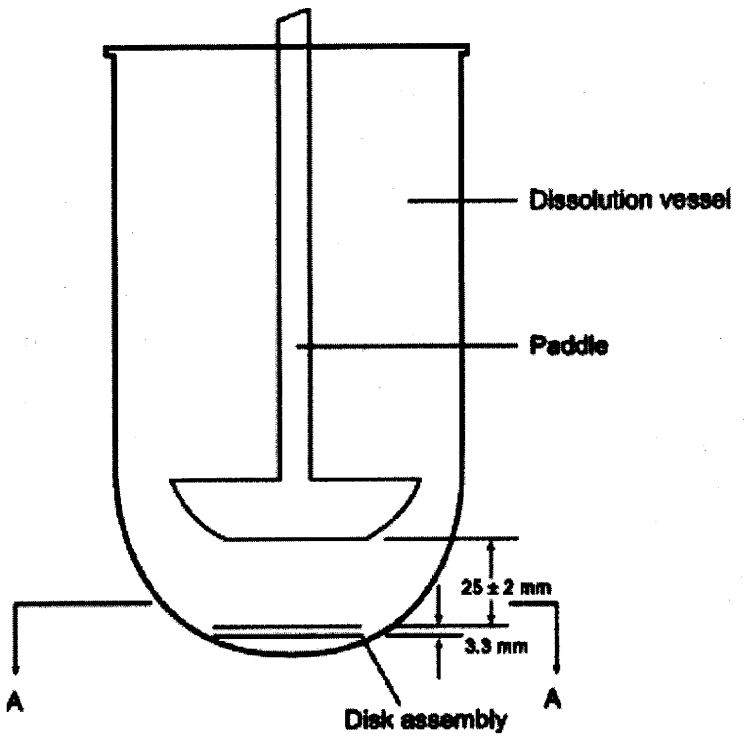


図2　パドルとディスクの配置

シリンダー法

1．　シリンダー法の装置（装置５）

装置は、溶出試験法<6.10>のパドル法の装置のうち、ベッセルはそのまま使用し、パドルは図２に示すシリンダー回転部品に置き換えて試験を行う。製剤は、試験の開始時にシリンダー側面に貼り付ける。ベッセル底部とシリンダー下部の距離は、、通例、25 ± 2 mm とする。試験液の温度は 32 ± 0.5 ℃の一定に保つ。
ベッセルはできるだけ試験液の蒸発を防ぐように蓋をする。

2．シリンダー法の操作

規定された量の試験液をベッセルに入れ、規定の温度になるまで待つ。試験液として、通例、pH5～7 の範囲における任意の緩衝液を用いる。また、製剤の形状に影響を与えなければ水－アルコール混液、有機溶媒等を用いることができる。

製剤から保護シートを取り除き、必要に応じて、粘着面を製剤よりも 1cm 以上大きな多孔性の膜に貼り付ける。シリンダーに製剤を貼り付けるには二つの方法がある。

-はみ出した多孔性膜に粘着剤を塗り,必要に応じて製剤の背面にも粘着剤を塗る。
-両面テープをシリンダーの外側に貼る。

注意深く、製剤の粘着面でない方をシリンダー側面に貼り付け、放出面が試験液に接するように、製剤の長軸がシリンダーの周囲を囲むように貼り付ける。
粘着剤や両面テープは、あらかじめ分析を妨害したり、有効成分を吸着しないことを確認しておく必要がある。
シリンダーを溶出試験装置に取り付け、すみやかに規定された回転数でシリンダーを回転させる。規定された時間間隔あるいは規定された時間に、試験液面とシリンダーの低部の間で、壁面から 1cm 以上離れたところから試験液を採取する。

規定された分析法で、溶出した有効成分量を測定する。その也の試料についても同様の操作を行う。

判定法　試験液採取時間における製剤からの放出率は規格範囲内である。

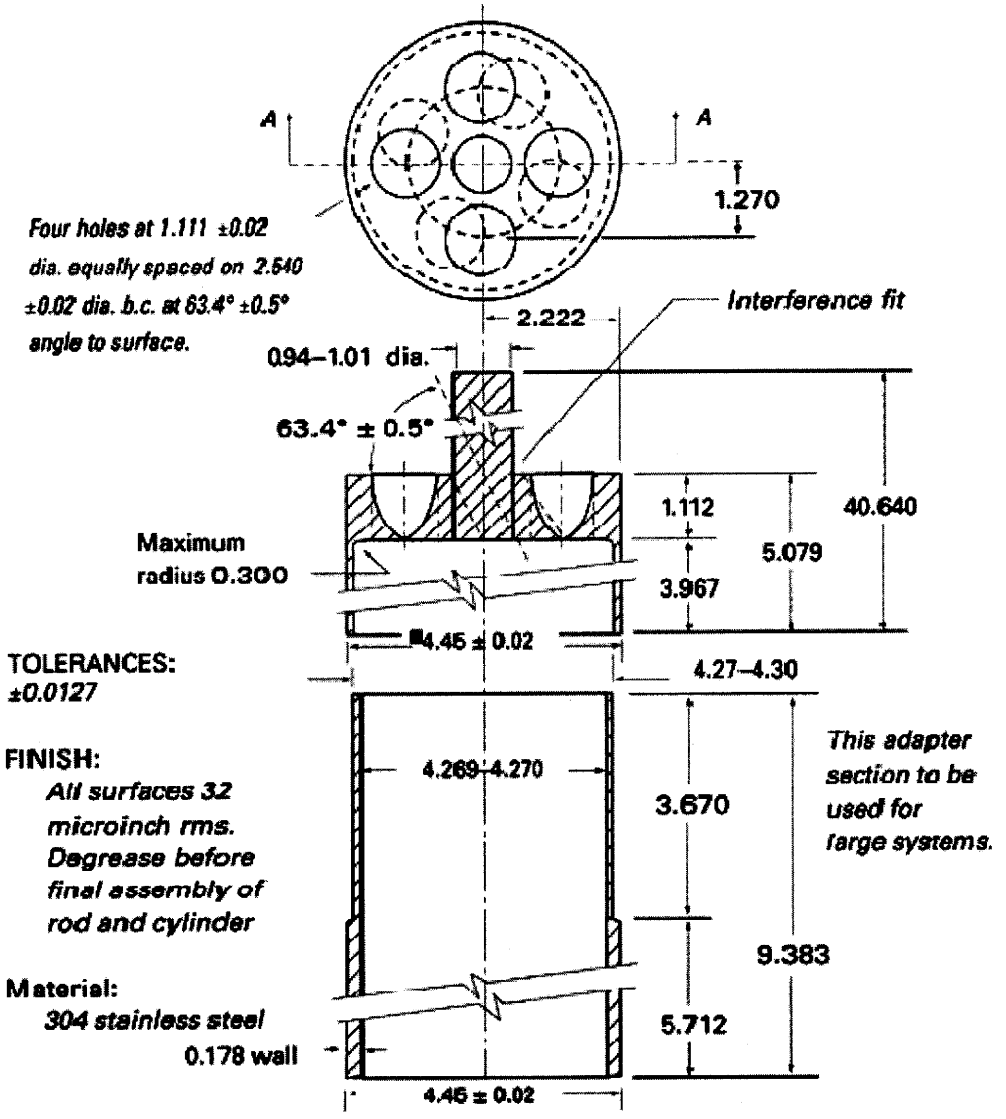


図２　シリンダー回転部品（単位は cm）

研究成果の刊行

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
川口正美，梶村計志，田口修三	トコフェロールニコチン酸エステルカプセルにおける溶出挙動の経時変化に関する検討	医薬品医療機器レギュラトリーサイエンス	42	149-155	2011
四方田千佳子	ジェネリック医薬品を語るための知識(2)	ファーマテクジャパン	26	909-913	2010
四方田千佳子	後発医薬品の品質検証はどう行われているのか	月刊薬事	52	1457-1464	2010
四方田千佳子，柴田寛子	ジェネリック医薬品を語るための知識(3)	ファーマテクジャパン	26	1861-1867	2010

投稿/原著

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トコフェロールニコチン酸エステルカプセルにおける溶出挙動の経時変化に関する検討

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Changes in Dissolution Behavior of Tocopherol Nicotinate Capsules during Storage

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Summary

Many drugs have recently been recalled from the market because of dissolution problems. In the past three years, 27 cases of recall due to decreased dissolution rate after storage have been reported.

Dissolution seems more likely to be altered during storage than any other product requirement. Thus, we examined the changes in the dissolution of tocopherol nicotinate capsules during storage under various conditions, and investigated the causes of variations.

Four products were stored under 3 conditions (25℃/60% RH, 40℃/75% RH, and 25℃/75% RH), and dissolution tests were performed after 0, 3, and 6 months. Using 4 types of dissolution medium, dissolution curves were prepared according to the Orange Book (Japanese Edition).

After storage at 25℃/60% RH, 1 product did not pass the dissolution test. Furthermore, 2 other products showed changes of dissolution behavior from the results of quality reevaluation, although they still met their dissolution test requirements. Among the storage conditions examined, storage at 40℃/75% RH for 6 months caused marked changes, and the most marked differences among the products were observed in pH 1.2 dissolution medium.

When dissolution tests were performed with the capsule contents, there was no delay or reduction of dissolution after storage. Thus, dissolution tests under the same conditions were performed, using samples prepared by exchanging the capsular shells and contents with those of other products. The results indicated that the changes in the dissolution behavior of stored capsules were due to alterations in the capsular film or contents, or both.

Key words

Tocopherol nicotinate, Hard capsule, Dissolution behavior, Time-course changes, Storage test, Accelerated storage condition, Quality reevaluation, Japan edition of Orange Book

1. 緒 言

医薬品の品質を一定の水準に保つことを目的とした医療用内服固形製剤の品質再評価事業（平成10～19年度）が行われ，我が国で流通する大部分の後発医薬品に対して新たに溶出試験が設定された．溶出試験は，著しい生物学的非同等性を防ぐことを目的とする製剤試験であり，一定時間後に溶け出す薬効成分の量（溶出率）を *in vitro* において測定する．欧米では従来から，数多くの医薬品に適用されてきた．そのため，我が国では多くの製剤に設定されることが待望されてきた．

医薬品の製造販売承認申請には，安定性に関する資料

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の提出が求められ，通常の保存条件で一定期間，品質が安定なことが保証されている．しかし，品質再評価事業で新たに溶出試験が設定された製剤は，試験法及び溶出規格のみが設定され，溶出性に基づく品質が一定期間安定であることは確認されていない．平成19年に策定された「後発医薬品の安心使用促進アクションプログラム」(アクションプログラム)[1]では，承認時には必ずしも求められていない長期保存試験や無包装状態での安定性試験等の実施が，メーカーの取り組む課題として取りあげられている．しかし，平成21年度末時点においても，これらの試験が終了していない品目がある[2]．

一方，近年，溶出性が問題で市場から回収される医薬品が見受けられる．医薬品医療機器情報提供ホームページでは，医薬品の回収に関する情報が公表されているが[3]，2007～2010年度（2010.8.31現在）において，クラスⅡに該当する体外診断薬を除く医薬品の回収事例165件中，製品規格に不適となった事例は61件であった．そのうち，製造後数箇月経過した製品について，溶出率の低下を原因として回収を行った事例が27件，報告されている．これらはアクションプログラムに従い，各メーカーが長期保存試験等で，安定性の問題に取り組んでいることが理由の一つであると考えられる．しかし，溶出性を問題とした回収事例は先発医薬品にも認められており，製品規格の中で溶出性は変化が生じ不適となりやすい項目となっている．

本稿では，回収事例をもとに選定したトコフェロールニコチン酸エステル（TN）の硬カプセル剤について，経時的に溶出挙動を比較し，その変動の原因について検討した．

2. 実験方法

1. 検体

市場に流通しているTNを有効成分とする硬カプセル剤（含量100 mg）4製剤を用いた．製造8箇月後（製品Cは10箇月後）に製剤を購入し，1箇月室温で保管後，保存試験を開始した．使用期限は，A，B，Dの3製剤は2011年10月，製品Cは2011年8月，有効期間はすべて3年であった．なお，本稿で示す製造後の経過月数は使用期限と有効期間から逆算したものである．

2. 検体の保存条件

塩化ナトリウム又は臭化ナトリウムの飽和溶液を入れたデシケーター中に，PTP包装状態の製剤を入れ恒温槽で保存した[4,5]．保存条件は安定性試験ガイドライン等[6,7]を参考に，25℃，60%RHの長期保存条件，40℃，75%RHの加速条件，湿度の評価用の中間条件として，25℃，75%RHの3条件を設定した．

3. 試薬

ニコチン酸（±）-α-トコフェロール（生化学用；純度98.8%）；和光純薬工業製，日本薬局方トコフェロールニコチン酸エステル標準品（純度；98.9%）；日本公定書協会製，ドデシル硫酸ナトリウム（等級なし）：東京化成工業製，その他の試薬は和光純薬工業製（試薬特級）を用いた．

4. 溶出試験条件

保存検体について，保存開始0，3，6箇月後に溶出試験を実施した．溶出試験機はDT-810 Dissolution Testerシステム　日本分光製を用いた．溶出試験の条件は，日本薬局方外医薬品規格第三部[8]に従い，パドル法，毎分100回転で，シンカーを使用した．試験液は，医療用医薬品品質情報集[9]（オレンジブック）に溶出曲線が収載されている4種類の試験液（pH 1.2：溶出試験第1液[10]，pH 4.0：pH 4.0の0.05 mol/L酢酸・酢酸ナトリウム緩衝液[10]，pH 6.8：薄めたMcIlvaine緩衝液，水，すべてラウリル硫酸ナトリウムを0.2%含有）を用いた．また，溶出試験開始5，10，15，30，45，60分後の試験液を採取し，オレンジブックの方法で溶出率を算出し，溶出曲線を作成した．なお，溶出率はすべてn=6の平均値とした．

5. HPLC測定条件[6]

高速液体クロマトグラフは島津製作所製Prominenceシリーズ又はCLASS-VPシリーズを用いて，測定波長；264 nm，カラム；YMC-Pack ODS A-302（4.6×150 mm，5 μm），カラム温度；40℃，移動相；メタノール，流速；1.0 mL/min，注入量；10 μLで行った。

3. 実験結果

1. 長期保存条件（25℃60%RH）における溶出挙動の変化

1)　pH 6.8の試験液を用いて溶出挙動を確認した結果，製品A，C，Dについては，経時的な変化はほとんど認められなかった（Fig. 1）．

しかし，製品Bは，保存3箇月の時点で，15分後の平均溶出率が65%に低下した．TNカプセルは，pH 6.8の試験液を用い，溶出開始15分後に70%以上の溶出率を示すことが製品規格に定められている．そこで，公的溶出試験に従い，溶出開始15分後に試験液を採取する

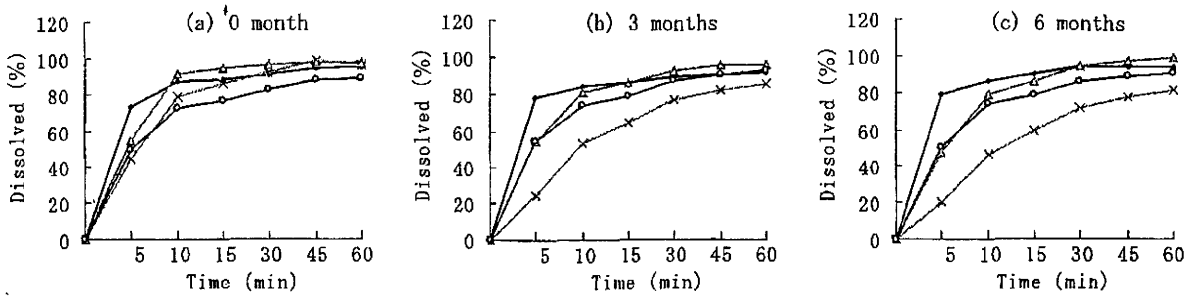

Fig. 1 Time-course Change of Dissolution Behavior under the Storage Condition at 25℃ 60%RH (pH 6.8)
Product A (◆), Product B (×), Product C (△), Product D (○)

方法で溶出率を確認したが，溶出率は，同様に65%の値を示した．

今回の検討は，紙箱から取り出した製品を用いており，承認審査時に要求されている市販状態の製品を評価したものとは異なっている．なお，その後製品Bは，製造メーカーの保存品においても溶出規格にも逸脱が認められ，同一製造方法の複数ロット製品について回収が行われ，同時に製造中止となっており，現在は流通していない．

2) pH 6.8以外の試験液を用いて溶出挙動を確認した結果，経時的な溶出率の遅延や低下が認められた製品（B及びC）と，ほとんど認められない製品（A及びD）が存在した（Fig. 2）．

製品B及びCは，pH 1.2の試験液を用いたとき，溶出

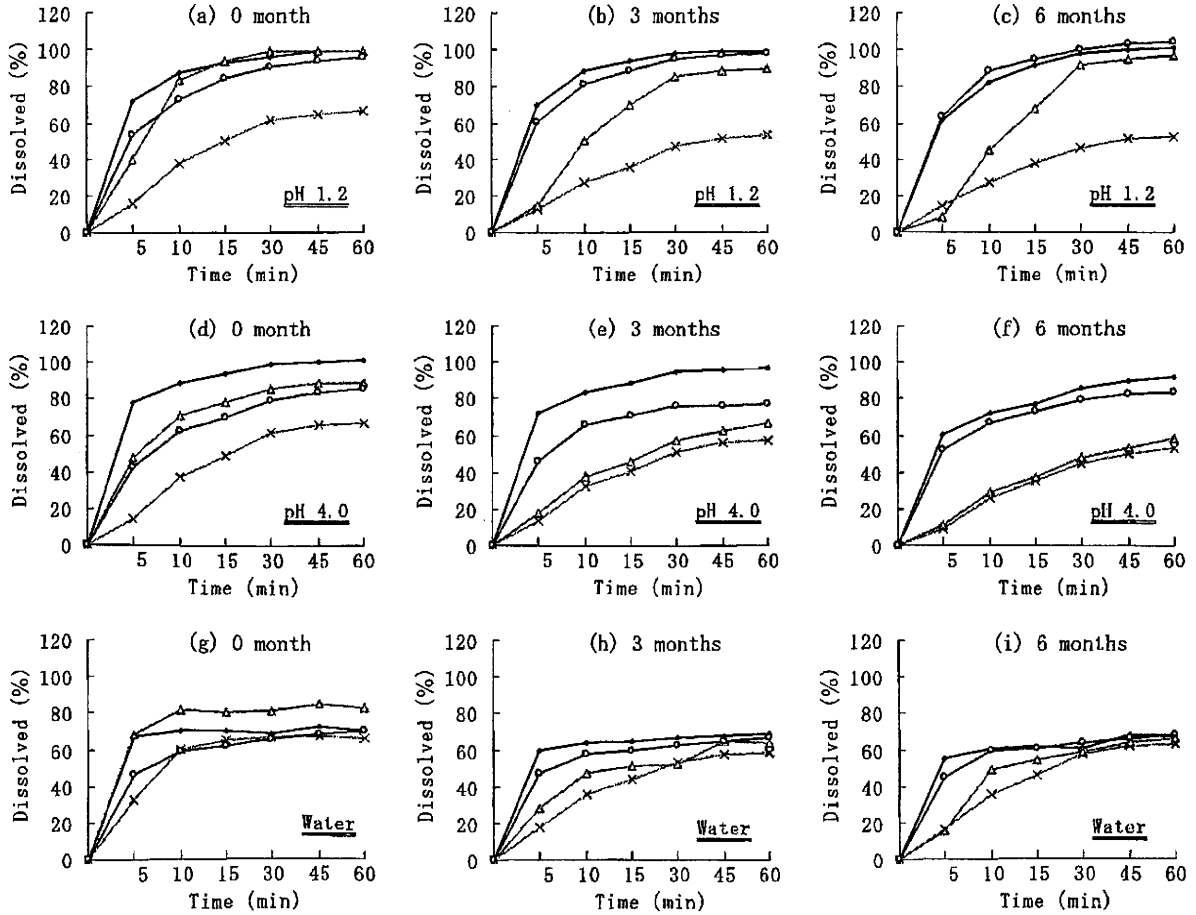

Fig. 2 Time-course Change of Dissolution Behavior under the Storage Condition at 25℃ and 60%RH (pH 1.2, pH 4.0, and water)
Product A (◆), Product B (×), Product C (△), Product D (○)

率の低下と遅延がそれぞれ認められ，pH 4.0 の試験液を用いたとき，溶出率の低下が認められた．製品 C では，試験液に水を用いたときにも，溶出率の低下及び遅延が認められた．

pH 4.0 の試験液を用いたときは，0 箇月時点で製品間の溶出挙動に差が認められた．6 箇月保存後の製品 A は，溶出率の低下が若干認められたが，製品 B 及び C と比較するとその差は小さかった．

試験液に水を用いたときは，製品 C 以外でもわずかに溶出率の低下が認められたが，6 箇月保存後の試験液採取時間 30 分以降については製品間の差はなかった．

2. 保存条件の違いによる溶出挙動の比較

各製剤を 3 種類の条件で 6 箇月間保存し，溶出挙動を比較した．

保存条件が苛酷な程，試験液の違いにかかわらず，溶出率の遅延が認められた (Fig. 3)．製品 A 以外は，保存条件 40℃75%RH では，すべての試験液で，5 分後の溶出率が 10%以下であり，保存開始時と比較すると，著しく低下していた．製品 B 及び C は，保存条件にかか

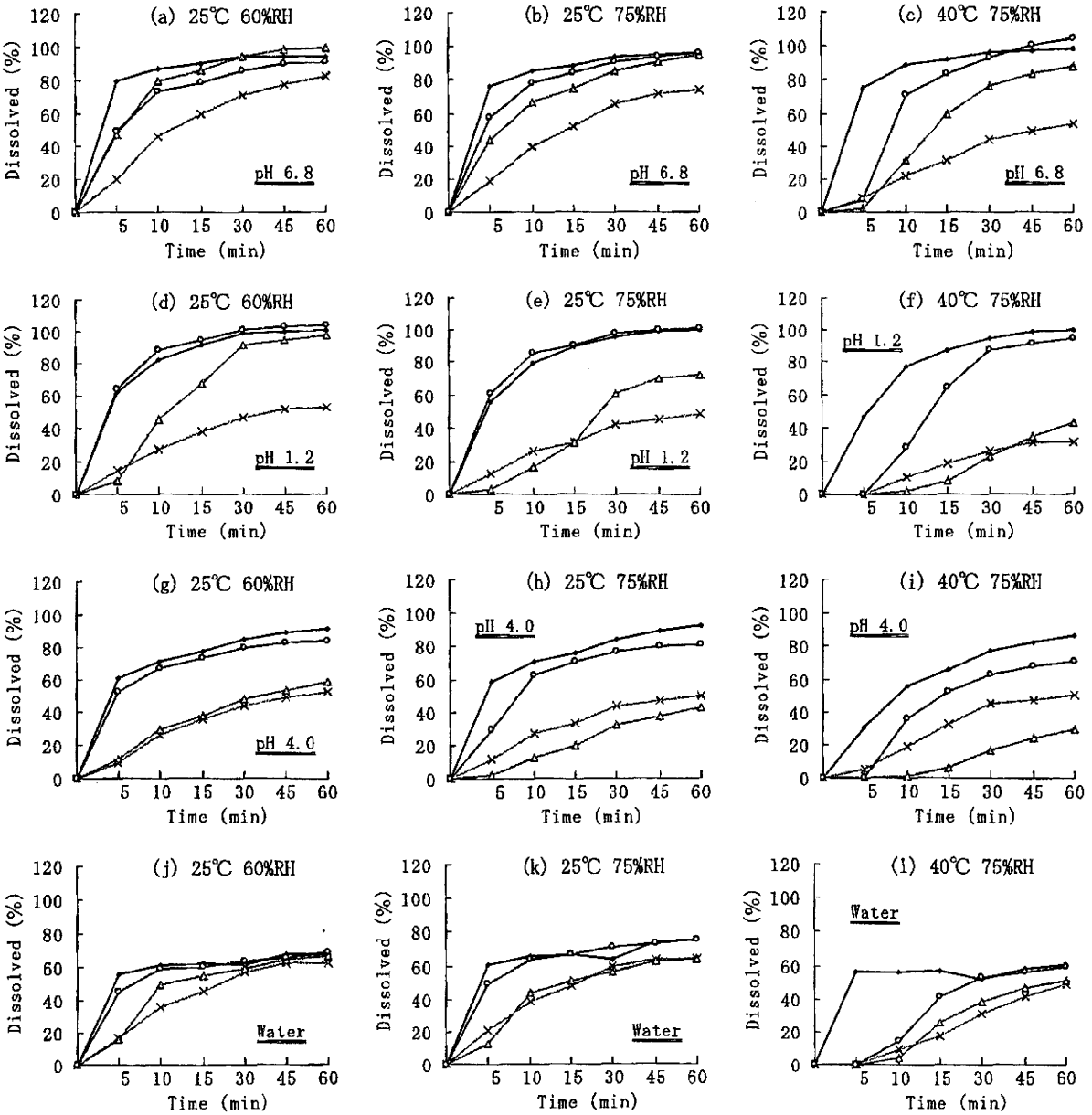

Fig. 3 Change of Dissolution Behavior after stored for 6 months in Different Conditions (pH 6.8, pH 1.2, pH 4.0, and water)

Product A (◆), Product B (×), Product C (△), Product D (○)

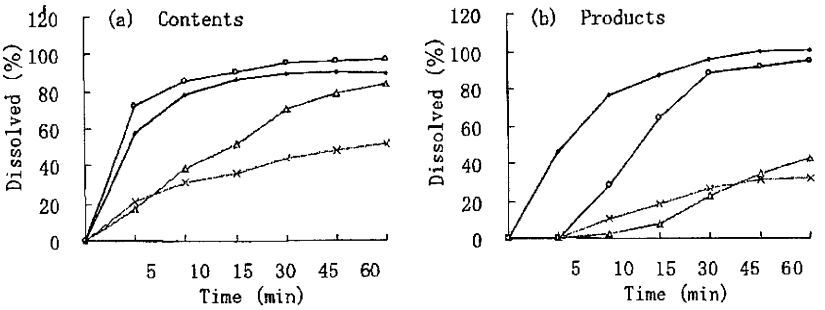

Fig. 4 Difference in Dissolution Behavior of Contents and Products
A (◆), B (×), C (△), D (○)

わらず，溶出率の低下が顕著に認められた．

製品A及びDは，温度の影響を受け，溶出率の若干の遅延や低下が起こる傾向があった．

3. 製剤内容物による溶出挙動

加速条件における6箇月保存後の各製剤において，製品A以外は，溶出率の低下や溶出挙動の遅延等の変化が認められたため，カプセルを開封し，内容物の溶出挙動を確認した（Fig. 4(a)）．なお，検討に用いた試験液は各製剤間の溶出挙動の差が最も大きいpH 1.2の条件とした．

内容物単独の溶出挙動を6箇月保存後の製剤（Fig. 4(b)）と比較すると，製品B及びCでは溶出率が全体的に高くなり，製品Dでは溶出の遅延は解消された．

また試験開始時の製剤（Fig. 2(a)）との比較では，製品B及びCは，溶出率の低下が認められ，特に，60分後の溶出率は15%以上低下した．一方，製品Dでは，内容物単独の溶出率に低下や遅延は認められず，保存開始時の製剤と溶出挙動に差はなかった．製品Aはやや低めではあるが，保存後の内容物と保存開始直後の製剤に差はなかった．

4. 再充てん試料を用いた溶出挙動の比較

製品B，C，Dのカプセル外皮の変化が溶出率の遅延の原因であるかどうかを明確に確認するため，各製品の内容物を入れ替えた試料（各製剤を開封し，その内容物を取り出し，空にした製剤のカプセルに取り出した内容物を再充てんした試料）を作成し，pH 1.2の試験液により溶出試験を実施した．試料は，それぞれの組合せから試料1～10とした（Table 1）．なお，カプセルと内容物の組合せによっては，1カプセル分の内容物を全量充てんすることができなかったため，すべての組合せについて，各内容物の90～93%の範囲で充てんした．

40℃75%RHで保存後に溶出挙動の低下が認められた製品Bと，溶出挙動に変化が認められなかった製品Aを用い，カプセル及び内容物を組合せて検討を行った（試料1，2，5，6）．その結果，内容物が同じであればカプセルの違いにかかわらず，溶出挙動に差はなく，内容物の違いに基づく2パターンの溶出曲線が得られた（Fig. 5(a)）．

Table 1 Sample Combination

Sample No.	Content	Capsule Shell
1	Product A	Product A
2	Product A	Product B
3	Product A	Product C
4	Product A	Product D
5	Product B	Product A
6	Product B	Product B
7	Product C	Product A
8	Product C	Product C
9	Product D	Product A
10	Product D	Product D

同様に，溶出率の低下が認められた製品Cと製品Aの組合せ（試料1，3，7，8）は，内容物が製品Aの場合，カプセルの違いはないものの，カプセルCの場合は，内容物の違いにより，溶出開始は遅いが一定時間経過後は溶出が進む曲線と，試験開始から緩やかに溶出を続ける曲線を示した（Fig. 5(b)）．

一方，40℃75%RHで保存後に溶出率の遅延が認められた製品Dと，変化がなかった製品Aの組合せ（試料1，4，9，10）は，カプセルの違いにより，異なる溶出曲線が得られた．すなわち，カプセルDに内容物Aを再充てんした場合（試料4）は，製品Dと同様に溶出の遅延が認められたが，カプセルAに内容物Dを再充てんした場合（試料9）は，溶出率の遅延は改善された（Fig. 5(c)）．

4. 考　察

四方田らは，PTPシート保管後の溶出率の低下が原薬の吸湿による水和物の生成によることが示唆される事例を報告している[10]．しかし，本製剤の有効成分である

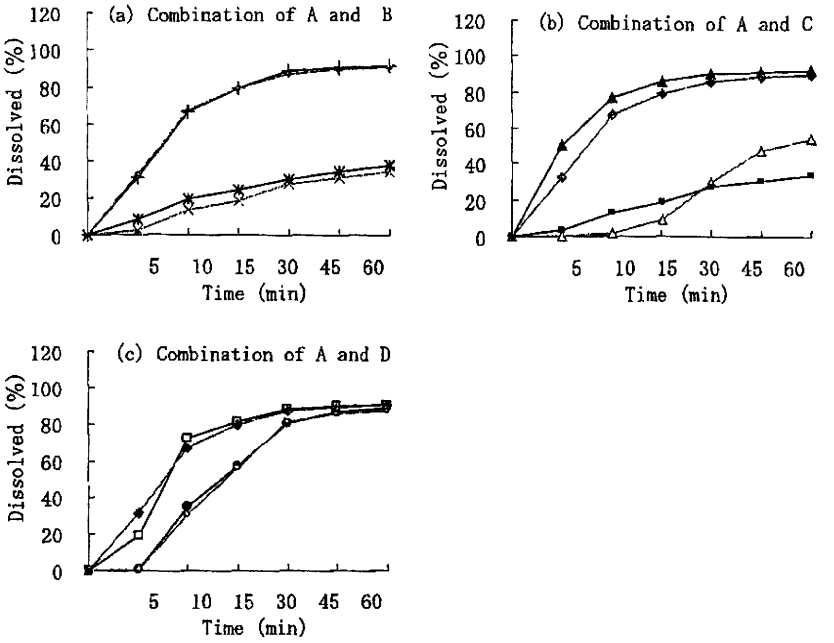

Fig. 5 Comparison of Dissolution Behavior on Combination of Contents and Capsule Shells

(a) Content A—Capsule Shell A (◆), Content A—Capsule Shell B (+), Content B—Capsule Shell A (✳), Content B—Capsule Shell B (×)
(b) Content A—Capsule Shell A (◆), Content A—Capsule Shell C (▲), Content C—Capsule Shell A (■), Content C—Capsule Shell C (△)
(c) Content A—Capsule Shell A (◆), Content A—Capsule Shell D (●), Content D—Capsule Shell A (□), Content D—Capsule Shell D (○)

TNは吸湿性がほとんどないため[9]，水和物生成の可能性はきわめて低い．また，溶出率の低下した製剤は，保存開始直後と比較して，含量の低下は認められなかったことを確認しており，少なくとも有効成分の安定性に問題はなかった．

今回検討を行った硬カプセル剤は，添付文書等に，ゼラチンを原料としていることが記載されている．ゼラチンを含有する硬カプセル剤は，加速試験等の条件において，溶出性が低下する場合があることが知られている[12]．

硬カプセル剤の溶出試験において，有効成分が溶出するには，カプセル皮膜がすべて溶解する必要はなく，一部が崩壊して内容物が皮膜の外に出て有効成分が溶出するか，カプセル内部に試験液が入り，成分が溶解した液が容器内に拡散することでもたらされる．保存試料の検討では，溶出試験終了時に，カプセル皮膜に内容物が付着した状態で，シンカーの編み目部分にこびりついたように残留していた試料も散見された．このような試料は，最終の溶出率が低い傾向にあったことから，溶解や崩壊が不十分なカプセル皮膜と内容物が密着し，内容物と溶出試験液が十分に接触しなかったことが考えられる．

製品Dについては，保存後の製剤からカプセルを除くことや，40℃75%RHの条件下で6箇月保存後も変化が認められなかった製品Aのカプセルに内容物を詰め替えることにより，溶出率の遅延は改善されている．このことから，カプセル剤皮が保存の影響を受け，溶出率の遅延が生じたと考えられる．

製品Bでは，保存後の製品AとBのカプセル外皮に，それぞれの内容物を詰め替えると，カプセルの違いには関わらず，内容物の違いに基づく，2種類の溶出曲線を示している．このことから，溶出率の低下はカプセル皮膜ではなく，内容物の変化が主な原因であると考えられる．

製品Cでは経時的に変化が認められたが，内容物単独では，保存後の製剤に比較すると溶出率が高く，また，速く溶出する挙動を示している．しかし，保存開始前の製剤と比較すると，溶出率が低く，遅延も認められる．再充てんした試料の溶出曲線において，内容物Aを充てんした試料3であれば，有効成分の速やかな溶解が認められた．製品Cの溶出率の低下については，カプセル皮膜の若干の変性に加え，内容物が変化したことが原因であると考えられる．

また，溶出試験実施の際，製品A及びDの内容物は，カプセルの崩壊直後に，パドルの回転によって溶出試験液の中に広がった．一方，保存後の製品B及びCは，カ

プセルの崩壊部分からこぼれ落ちた内容物が，シンカーの付近で回転し，溶出試験液全体に広がることはなく，また，内容物の一部分は堆積していた．内容物単独の場合では，試料の投入後，山のように内容物が堆積し，その堆積物は試験終了時にも存在していた．

小和田らは，製剤の崩壊直後，試料が堆積し溶出率が低くなる事例を報告しているが[13]，今回の検討に用いた製品B及びCにおいても，試料の内容物の堆積が溶出率の低下を招いていることが推測された．

しかしながら，カプセル皮膜の残留や内容物の堆積は，保存開始直後の製剤の溶出試験実施時にはほとんど認められなかったことから，溶出率の低下には，堆積が生じるような内容物の変化とともに，保存試験開始時と比較して溶解しにくくなったカプセルの影響を受けていると推察される．

今回の検討結果は，医薬品の規格試験方法として設定されている試験液（pH 6.8）では，回収事例となった製剤以外は，製品間の差は少ないものの，pH 1.2及びpH 4.0の試験液については，製品間の差が顕著に表れている．また，最も緩和な保存条件である25℃60%RHにおける6箇月後の溶出挙動の差は，pH 1.2，pH 4.0，pH 6.8，水の順に，小さくなっているが，TNの37℃における試験液への溶解度も同様に低下している[9]．

現在，各製品の溶出挙動は，実生産規模品において定期的に確認することがアクションプログラムに示されているものの，日常的に管理することは要求されていない．しかし，今回の結果は，ジェネリック検討委員会報告でアマンタジン塩酸塩錠等の溶出挙動について示された結果と同様に[14]，品質再評価後の溶出性が変化していることを示している．更に，保存状態によっては，溶出挙動が経時的に変化する製剤もあることや，試験液の違いによって，より明確になる場合があることも示している．

これらのことから，日常的に管理が必要なpH 6.8の試験液を用いた一時点の評価だけでなく，他の試験液も含め溶出挙動の経時的な変化を評価することは，溶出性に係る変化を的確に捉えることができるのではないかと推察される．

5. 結　論

各種条件による保存試験の結果，製品規格に設定された試験液における溶出試験には適合しているが，品質再評価時の溶出挙動から変化が認められた製剤が存在した．その原因は，有効成分の含量低下等に由来するものではなく，カプセル皮膜又は内容物の変化，あるいはその両方に起因するものであった．

今後は，品質再評価時のデータを生かし，保存ロットに対しても，さまざまな試験液を用いた評価を行い，そのデータを蓄積し，更なる品質の向上を目指すとともに，溶出性の変化を的確に評価する必要があると考えられる．

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