last addition of solution, begin rinsing the inner walls of the filter holder by using a jet of *particle-free water*. Maintain the vacuum until the surface of the membrane filter is free from liquid. Place the membrane filter in a Petri dish, and allow the membrane filter to air-dry with the cover slightly ajar. After the membrane filter has been dried, place the Petri dish on the stage of the microscope, scan the entire membrane filter under the reflected light from the illuminating device, and count the number of particles that are equal to or greater than 10 µm and the number of particles that are equal to or greater than 25 µm. Alternatively, partial membrane filter count and determination of the total filter count by calculation is allowed. Calculate the mean number of particles for the preparation to be examined.

The particle sizing process with the use of the circular diameter graticule is carried out by estimating the equivalent diameter of the particle in comparison with the 10 µm and 25 µm reference circles on the graticule. Thereby the particles are not moved from their initial locations within the graticule field of view and are not superimposed on the reference circles for comparison. The inner diameter of the transparent graticule reference circles is used to size white and transparent particles, while dark particles are sized by using the outer diameter of the black opaque graticule reference circles.

In performing the *Microscopic Particle Count Test,* do not attempt to size or enumerate amorphous, semiliquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane filter. These materials show little or no surface relief and present a gelatinous or film-like appearance. In such cases, the interpretation of enumeration may be aided by testing a sample of the solution by the *Light Obscuration Particle Count Test*.

Evaluation

For preparations supplied in containers with a nominal volume of more than 100 mL, apply the criteria of *Test 2.A*.

For preparations supplied in containers with a nominal volume of less than 100 mL, apply the criteria of *Test 2.B*.

For preparations supplied in containers with a nominal volume of 100 mL, apply the criteria of *Test 2.B*. [NOTE—*Test 2.A* is used in the *Japanese Pharmacopeia.*]

Test 2.A *(Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of more than 100 mL)*—The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per mL equal to or greater than 10 µm and does not exceed 2 per mL equal to or greater than 25 µm.

Test 2.B *(Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL)*—The preparation complies with the test if the average number of particles present in the units tested does not exceed 3000 per container equal to or greater than 10 µm and does not exceed 300 per container equal to or greater than 25 µm.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	Desmond G. Hunt, Ph.D. Senior Scientific Liaison 1-301-816-8341	(GCDF2010) General Chapters - Dosage Forms

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Table 2.9.18.-9. – *Calculations for Apparatus E. Use q = (60/Q)^x, where Q is the test flow rate in litres per minute, and x is listed in the table*

Cut-off diameter (µm)	x	Mass of active substance deposited per discharge	Cumulative mass of active substance deposited per discharge	Cumulative fraction of active substance (per cent)
$d_7 = 0.34 \times q$	0.67	mass from MOC or terminal filter, m_8	$c_7 = m_8$	$F_7 = (c_7/c) \times 100$
$d_6 = 0.55 \times q$	0.60	mass from stage 7, m_7	$c_6 = c_7 + m_7$	$F_6 = (c_6/c) \times 100$
$d_5 = 0.94 \times q$	0.53	mass from stage 6, m_6	$c_5 = c_6 + m_6$	$F_5 = (c_5/c) \times 100$
$d_4 = 1.66 \times q$	0.47	mass from stage 5, m_5	$c_4 = c_5 + m_5$	$F_4 = (c_4/c) \times 100$
$d_3 = 2.82 \times q$	0.50	mass from stage 4, m_4	$c_3 = c_4 + m_4$	$F_3 = (c_3/c) \times 100$
$d_2 = 4.46 \times q$	0.52	mass from stage 3, m_3	$c_2 = c_3 + m_3$	$F_2 = (c_2/c) \times 100$
$d_1 = 8.06 \times q$	0.54	mass from stage 2, m_2	$c_1 = c_2 + m_2$	$F_1 = (c_1/c) \times 100$
		mass from stage 1, m_1	$c = c_1 + m_1$	100

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2.9.19. PARTICULATE CONTAMINATION: SUB-VISIBLE PARTICLES

Particulate contamination of injections and infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

For the determination of particulate contamination 2 procedures, Method 1 (Light Obscuration Particle Count Test) and Method 2 (Microscopic Particle Count Test), are specified hereinafter. When examining injections and infusions for sub-visible particles, Method 1 is preferably applied. However, it may be necessary to test some preparations by the light obscuration particle count test followed by the microscopic particle count test to reach a conclusion on conformance to the requirements.

Not all parenteral preparations can be examined for sub-visible particles by one or both of these methods. When Method 1 is not applicable, e.g. in case of preparations having reduced clarity or increased viscosity, the test is carried out according to Method 2. Emulsions, colloids, and liposomal preparations are examples. Similarly, products that produce air or gas bubbles when drawn into the sensor may also require microscopic particle count testing. If the viscosity of the preparation to be tested is sufficiently high so as to preclude its examination by either test method, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary, to allow the analysis to be performed.

The results obtained in examining a discrete unit or group of units for particulate contamination cannot be extrapolated with certainty to other units that remain untested. Thus, statistically sound sampling plans must be developed if valid inferences are to be drawn from observed data to characterise the level of particulate contamination in a large group of units.

METHOD 1. LIGHT OBSCURATION PARTICLE COUNT TEST

Use a suitable apparatus based on the principle of light blockage which allows an automatic determination of the size of particles and the number of particles according to size.

The apparatus is calibrated using suitable certified reference materials consisting of dispersions of spherical particles of known sizes between 10 µm and 25 µm. These standard particles are dispersed in *particle-free water R*. Care must be taken to avoid aggregation of particles during dispersion.

General precautions

The test is carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Very carefully wash the glassware and filtration equipment used, except for the membrane filters, with a warm detergent solution and rinse with abundant amounts of water to remove all traces of detergent. Immediately before use, rinse the equipment from top to bottom, outside and then inside, with *particle-free water R*.

Take care not to introduce air bubbles into the preparation to be examined, especially when fractions of the preparation are being transferred to the container in which the determination is to be carried out.

In order to check that the environment is suitable for the test, that the glassware is properly cleaned and that the water to be used is particle-free, the following test is carried out: determine the particulate contamination of 5 samples of *particle-free water R*, each of 5 ml, according to the method described below. If the number of particles of 10 µm or greater size exceeds 25 for the combined 25 ml, the precautions taken for the test are not sufficient. The preparatory steps must be repeated until the environment, glassware and water are suitable for the test.

Method

Mix the contents of the sample by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of *particle-free water R* and remove the closure, avoiding any contamination of the contents. Eliminate gas bubbles by appropriate measures such as allowing to stand for 2 min or sonicating.

For large-volume parenterals, single units are tested. For small-volume parenterals less than 25 ml in volume, the contents of 10 or more units are combined in a cleaned container to obtain a volume of not less than 25 ml; where justified and authorised, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 ml with *particle-free water R* or with an appropriate solvent without contamination of particles when *particle-free water R* is not suitable. Small-volume parenterals having a volume of 25 ml or more may be tested individually.

Powders for parenteral use are reconstituted with *particle-free water R* or with an appropriate solvent without contamination of particles when *particle-free water R* is not suitable.

The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals or for small-volume parenterals having a volume of 25 ml or more, fewer than 10 units may be tested, based on an appropriate sampling plan.

Remove 4 portions, each of not less than 5 ml, and count the number of particles equal to or greater than 10 µm and 25 µm. Disregard the result obtained for the first portion, and calculate the mean number of particles for the preparation to be examined.

Evaluation

For preparations supplied in containers with a nominal volume of more than 100 ml, apply the criteria of test 1.A.

For preparations supplied in containers with a nominal volume of less than 100 ml, apply the criteria of test 1.B.

For preparations supplied in containers with a nominal volume of 100 ml, apply the criteria of test 1.B

If the average number of particles exceeds the limits, test the preparation by the microscopic particle count test.

Test 1.A – Solutions for infusion or solutions for injection supplied in containers with a nominal content of more than 100 ml

The preparation complies with the test if the average number of particles present in the units tested does not exceed 25 per millilitre equal to or greater than 10 µm and does not exceed 3 per millilitre equal to or greater than 25 µm.

Test 1.B – Solutions for infusion or solutions for injection supplied in containers with a nominal content of less than 100 ml

The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 µm and does not exceed 600 per container equal to or greater than 25 µm.

METHOD 2. MICROSCOPIC PARTICLE COUNT TEST

Use a suitable binocular microscope, filter assembly for retaining particulate contamination and membrane filter for examination.

The microscope is equipped with an ocular micrometer calibrated with an objective micrometer, a mechanical stage capable of holding and traversing the entire filtration area of the membrane filter, 2 suitable illuminators to provide episcopic illumination in addition to oblique illumination, and is adjusted to 100 ± 10 magnifications.

The ocular micrometer is a circular diameter graticule (see Figure 2.9.19.-1) and consists of a large circle divided by crosshairs into quadrants, transparent and black reference circles 10 µm and 25 µm in diameter at 100 magnifications, and a linear scale graduated in 10 µm increments. It is calibrated using a stage micrometer that is certified by either a domestic or international standard institution. A relative error of the linear scale of the graticule within ± 2 per cent is acceptable. The large circle is designated the graticule field of view (GFOV).

2 illuminators are required. One is an episcopic brightfield illuminator internal to the microscope, the other is an external, focusable auxiliary illuminator adjustable to give reflected oblique illumination at an angle of 10-20°.

The filter assembly for retaining particulate contamination consists of a filter holder made of glass or other suitable material, and is equipped with a vacuum source and a suitable membrane filter.

The membrane filter is of suitable size, black or dark grey in colour, non-gridded or gridded, and 1.0 µm or finer in nominal pore size.

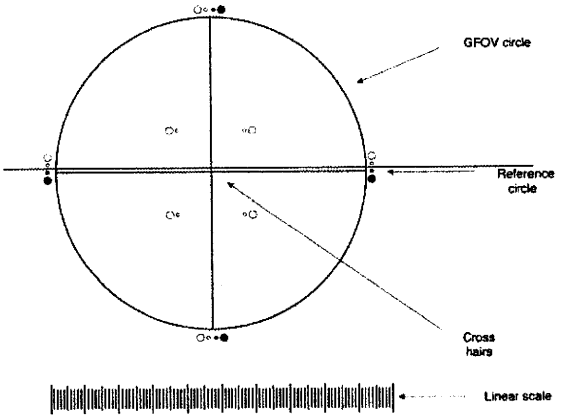

Figure 2.9.19.-1. – *Circular diameter graticule*

General precautions

The test is carried out under conditions limiting particulate contamination, preferably in a laminar-flow cabinet.

Very carefully wash the glassware and filter assembly used, except for the membrane filter, with a warm detergent solution and rinse with abundant amounts of water to remove all traces of detergent. Immediately before use, rinse both sides of the membrane filter and the equipment from top to bottom, outside and then inside, with *particle-free water R*.

In order to check that the environment is suitable for the test, that the glassware and the membrane filter are properly cleaned and that the water to be used is particle-free, the following test is carried out: determine the particulate contamination of a 50 ml volume of *particle-free water R* according to the method described below. If more than 20 particles 10 µm or larger in size or if more than 5 particles 25 µm or larger in size are present within the filtration area, the precautions taken for the test are not sufficient. The preparatory steps must be repeated until the environment, glassware, membrane filter and water are suitable for the test.

Method

Mix the contents of the samples by slowly inverting the container 20 times successively. If necessary, cautiously remove the sealing closure. Clean the outer surfaces of the container opening using a jet of *particle-free water R* and remove the closure, avoiding any contamination of the contents.

For large-volume parenterals, single units are tested. For small-volume parenterals less than 25 ml in volume, the contents of 10 or more units are combined in a cleaned container; where justified and authorised, the test solution may be prepared by mixing the contents of a suitable number of vials and diluting to 25 ml with *particle-free water R* or with an appropriate solvent without contamination of particles when *particle-free water R* is not suitable. Small-volume parenterals having a volume of 25 ml or more may be tested individually.

Powders for parenteral use are constituted with *particle-free water R* or with an appropriate solvent without contamination of particles when *particle-free water R* is not suitable.

The number of test specimens must be adequate to provide a statistically sound assessment. For large-volume parenterals or for small-volume parenterals having a volume of 25 ml or more, fewer than 10 units may be tested, based on an appropriate sampling plan.

Wet the inside of the filter holder fitted with the membrane filter with several millilitres of *particle-free water R*. Transfer to the filtration funnel the total volume of a solution pool or of a single unit, and apply vacuum. If needed, add stepwise a portion of the solution until the entire volume is filtered. After the last addition of solution, begin rinsing the inner walls of the filter holder by using a jet of *particle-free water R*. Maintain the vacuum until the surface of the membrane filter is free from liquid. Place the filter in a Petri dish and allow the filter to air-dry with the cover slightly ajar. After the filter has been dried, place the Petri dish on the stage of the microscope, scan the entire membrane filter under the reflected light from the illuminating device, and count the number of particles that are equal to or greater than 10 µm and the number of particles that are equal to or greater than 25 µm. Alternatively, partial filter count and determination of the total filter count by calculation is allowed. Calculate the mean number of particles for the preparation to be examined.

The particle sizing process with the use of the circular diameter graticule is carried out by transforming mentally the image of each particle into a circle and then comparing it to the 10 µm and 25 µm graticule reference circles. Thereby the particles are not moved from their initial locations within the graticule field of view and are not superimposed on the reference circles for comparison. The inner diameter of the transparent graticule reference circles is used to size white and transparent particles, while dark particles are sized by using the outer diameter of the black opaque graticule reference circles.

In performing the microscopic particle count test do not attempt to size or enumerate amorphous, semi-liquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane filter. These materials show little or no surface relief and present a gelatinous or film-like appearance. In such cases the interpretation of enumeration may be aided by testing a sample of the solution by the light obscuration particle count test.

Evaluation

For preparations supplied in containers with a nominal volume of more than 100 ml, apply the criteria of test 2.A.

For preparations supplied in containers with a nominal volume of less than 100 ml, apply the criteria of test 2.B.

For preparations supplied in containers with a nominal volume of 100 ml, apply the criteria of test 2.B.

Test 2.A – Solutions for infusion or solutions for injection supplied in containers with a nominal content of more than 100 ml

The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per millilitre equal to or greater than 10 µm and does not exceed 2 per millilitre equal to or greater than 25 µm.

Test 2.B – Solutions for infusion or solutions for injection supplied in containers with a nominal content of less than 100 ml

The preparation complies with the test if the average number of particles present in the units tested does not exceed 3000 per container equal to or greater than 10 µm and does not exceed 300 per container equal to or greater than 25 µm.

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2.9.20. PARTICULATE CONTAMINATION: VISIBLE PARTICLES

Particulate contamination of injections and infusions consists of extraneous, mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.

The test is intended to provide a simple procedure for the visual assessment of the quality of parenteral solutions as regards visible particles. Other validated methods may be used.

APPARATUS

The apparatus (see Figure 2.9.20.-1) consists of a viewing station comprising:

- a matt black panel of appropriate size held in a vertical position,
- a non-glare white panel of appropriate size held in a vertical position next to the black panel,
- an adjustable lampholder fitted with a suitable, shaded, white-light source and with a suitable light diffuser (a viewing illuminator containing two 13 W fluorescent tubes, each 525 mm in length, is suitable). The intensity of illumination at the viewing point is maintained between 2000 lux and 3750 lux, although higher values are preferable for coloured glass and plastic containers.

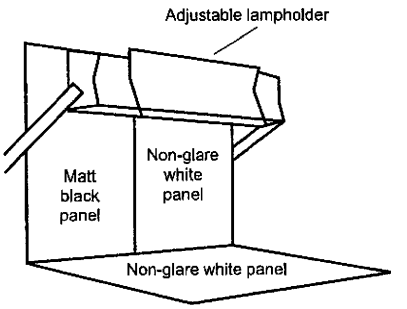

Figure 2.9.20.-1. – *Apparatus for visible particles*

METHOD

Remove any adherent labels from the container and wash and dry the outside. Gently swirl or invert the container, ensuring that air bubbles are not introduced, and observe for about 5 s in front of the white panel. Repeat the procedure in front of the black panel. Record the presence of any particles.

01/2008:20922

2.9.22. SOFTENING TIME DETERMINATION OF LIPOPHILIC SUPPOSITORIES

The test is intended to determine, under defined conditions, the time which elapses until a suppository maintained in water softens to the extent that it no longer offers resistance when a defined weight is applied.

APPARATUS A

The apparatus (see Figure 2.9.22.-1) consists of a glass tube 15.5 mm in internal diameter with a flat bottom and a length of about 140 mm. The tube is closed by a removable plastic cover having an opening 5.2 mm in diameter. The apparatus comprises a rod 5.0 mm in diameter which becomes wider

(xix) フォーゲル・ジョンソンカンテン培地

カゼイン製ペプトン	10.0g
酵母エキス	5.0g
D－マンニトール	10.0g
リン酸水素二カリウム	5.0g
塩化リチウム	5.0g
グリシン	10.0g
フェノールレッド	25mg
カンテン	16.0g
水	1000mL

全成分を混和した後，1分間煮沸して溶かす．121℃で15～20分間高圧蒸気滅菌後，45～50℃に冷却する．滅菌後のpH7.0～7.4．これに滅菌亜テルル酸カリウム溶液(1→100)20mLを加えて混和する．

(xx) ベアード・パーカーカンテン培地

カゼイン製ペプトン	10.0g
肉エキス	5.0g
酵母エキス	1.0g
塩化リチウム	5.0g
グリシン	12.0g
焦性ブドウ酸ナトリウム	10.0g
カンテン	20.0g
水	950mL

全成分を混和し，時々激しく振り混ぜながら加熱し，1分間煮沸する．121℃で15～20分間高圧蒸気滅菌した後，45～50℃に冷却する．滅菌後のpH6.6～7.0．これに滅菌亜テルル酸カリウム溶液(1→100)10mLと卵黄乳濁液50mLを加えて緩やかに混和した後，ペトリ皿に分注する．卵黄乳濁液は卵黄約30%，生理食塩液約70%の割合で混和して調製する．

(xxi) マンニット・食塩カンテン培地

カゼイン製ペプトン	5.0g
肉製ペプトン	5.0g
牛肉エキス	1.0g
D－マンニトール	10.0g
塩化ナトリウム	75.0g
フェノールレッド	25mg
カンテン	15.0g
水	1000mL

全成分を混和し，時々激しく振り混ぜながら加熱し，1分間煮沸した後，121℃で15～20分間高圧蒸気滅菌する．滅菌後のpH7.2～7.6.

3.3. 試薬・試液

(i) アムホテリシンB試液：アムホテリシンB粉末22.5mgを滅菌精製水9mLに溶かす．

アムホテリシンB粉末　アムホテリシンBにデオキシコール酸ナトリウムが添加されγ線滅菌されたもの．

(ii) 胆汁酸塩：動物の乾燥胆汁より製した黄褐色の粉末で，タウロコール酸ナトリウムやグリココール酸ナトリウムからなり，コール酸として45%以上を含む．5%水溶液のpHは5.5～7.5の範囲にある．

(iii) TTC試液：2,3,5－トリフェニル－2*H*－テトラゾリウム塩酸塩0.8gを水に溶かし100mLとする．小試験管などに小分けした後，121℃で15～20分間高圧蒸気滅菌する．遮光して保存する．

(iv) ローズベンガル試液：ローズベンガル1gを水に溶かし100mLとする．

ローズベンガル　$C_{20}H_2Cl_4I_4Na_2O_5$[特級]赤褐色の粉末で，水に溶けて紫赤色を示す．

3.4. 調製

(i) TTC添加カンテン培地の調製：滅菌したカンテン培地1L当たりTTC試液2.5～5mL(20～40mg/L)を使用直前に添加し，混和する．

(ii) アムホテリシンB添加カンテン培地の調製：121℃で15～20分間高圧蒸気滅菌したカンテン培地1L当たりアムホテリシンB試液2mL(5mg/L)を使用直前に添加し，混和する．

(iii) ローズベンガル試液添加カンテン培地の調製：カンテン培地1L当たりローズベンガル試液5mL(50mg/L)を添加し，混和後，121℃で15～20分間高圧蒸気滅菌する．

6. 製剤試験法

6.01 眼軟膏剤の金属性異物試験法

眼軟膏剤の金属性異物試験法は，製剤総則中の眼軟膏剤の金属性異物を試験する方法である．

1. 試料の調製

本剤10個につき，できるだけ清潔な場所で，5gずつを取り出し，それぞれを直径60mmの平底ペトリ皿に入れる．平底ペトリ皿にふたをし，85～110℃で2時間加熱して基剤を完全に溶かした後，揺り動かさないように注意しながら室温で放置し，固まらせる．内容量が5g未満の場合には，全量をなるべく完全に取り出し，同様に操作する．

2. 操作法

平底ペトリ皿を反転し，ミクロメーターの付いた40倍以上の倍率の顕微鏡を用い，光源を上方45°の角度より照射し，それぞれの平底ペトリ皿の底の50μm以上の金属性異物の数を数える．

試験に用いる平底ペトリ皿は，泡，きずなどがなく，内面の周縁と底面の角度がなるべく直角のものを用いる．

3. 判定

本剤10個の50μm以上の金属性異物の合計数は50個以下であり，かつ個々の平底ペトリ皿のうち金属性異物が8個を超えるものが1枚以下のときは適合とする．これに適合しないときは，更に20個について同様に試験し，本剤30個の金属性異物の合計が150個以下であり，かつ個々の平底ペトリ皿のうち金属性異物が8個を超えるものが3枚以下のときは適合とする．

6.02 製剤均一性試験法

本試験法は，三薬局方での調和合意に基づき規定した試験法である．

なお，三薬局方で調和されていない部分は「◆　◆」で囲むことにより示す．

製剤均一性試験法とは，個々の製剤の間での有効成分含量の

均一性の程度を示すための試験法である．したがって，本試験は，別に規定される場合を除き，単剤又は配合剤に含まれる個々の有効成分に対して適用される．

錠剤，カプセル剤，散剤又は顆粒剤の分包品，アンプル入り注射剤等は，個々の製剤中に有効成分の1回服用量又は複数個で1回用量になるように有効成分を含有している．そのような製剤の有効成分の含量の均一性を保証するには，ロット内の個々の製剤中の有効成分量が，表示量を中心とした狭い範囲内にあることを確認する必要がある．ただし，懸濁剤，乳剤又はゲルからなる外用の皮膚適用製剤へは本試験を適用しない．

製剤含量の均一性は，表6.02－1に示したように含量均一性試験又は質量偏差試験のいずれかの方法で試験される．含量均一性試験は，製剤個々の有効成分の含量を測定し，それぞれの成分の含量が許容域内にあるかどうかを確認する試験で，すべての製剤に適用できる．

質量偏差試験は次の製剤に適用できる．

(i) ◆成分が完全に溶解した◆液を個別容器に封入した製剤(軟カプセルを含む)．

(ii) 他の有効成分及び添加剤を含まず，単一の成分のみからなる散剤，顆粒及び用時溶解の注射剤などの固形製剤を個別容器に封入したもの．

(iii) ◆成分が完全に溶解した◆液を，最終容器内で凍結乾燥することにより製した用時溶解の注射剤などの固形製剤で，その調製法がラベル又は添付文書に記載されているもの．

(iv) 硬カプセル，素錠又はフィルムコーティング錠で，有効成分含量が25mg以上で，かつ製剤中の有効成分の割合が質量比で25%以上のもの．◆ただし，有効成分を含まない部分(コーティング部，カプセル殻など)を除いて計算する．◆ 25%より低い成分がある場合，その成分は含量均一性で試験する．

上記の条件を満たさない製剤は，含量均一性で試験する．ただし，(iv)に示された製剤で，25mg／25%の閾値に達しなかった場合でも，製造工程のバリデーション及び製剤開発のデータから最終製剤の有効成分の濃度の相対標準偏差(RSD)が2%以下であることが示され，試験法の変更が認められた場合には，質量偏差試験を適用できる．有効成分濃度RSDは，個々の製剤に対する有効成分濃度(w/w，w/v)のRSDで，個々の製剤中の有効成分含量を製剤質量で除することにより求められる．RSDの一般式は表6.02－2を参照．

1. 含量均一性試験

試料30個以上をとり，下記に示す方法に従って試験する．定量法と含量均一性試験とで異なる測定法を用いた場合には，補正係数が必要となる場合もある．

(i) 固形製剤：試料10個について個々の製剤中の有効成分含量を適切な方法で測定し，表6.02－2を参照して判定値を計算する．

(ii) 液剤：試料10個について，個々の容器から通常の使用法に従ってよく混合した内容物を取り出し，有効成分含量を測定し，表6.02－2を参照して判定値を計算する．

1.1. 判定値の計算

次の式に従って判定値を計算する．

$$|M-\bar{X}|+ks$$

記号は表6.02－2で定義される．

2. 質量偏差試験

◆本試験は，有効成分濃度(有効成分質量を製剤質量で割ったもの)が均一であるという仮定で行われる試験である．◆

適当な方法によりロットを代表する試料について測定し，有効成分の平均含量を求める．この値をAとし，判定値の計算の項で示したように，表示量に対する%として表す．試料30個以上をとり，下記に示す方法に従って試験する．

(i) 素錠又はフィルムコーティング錠：試料10個について個々の質量を精密に量り，定量法により求めた平均含量から，計算により個々の試料の含量推定値を求め，表示量に対する%で表す．判定値を計算する．

(ii) 硬カプセル剤：試料10個について，試料と質量の対応性に留意しながら，個々の質量をカプセルごと精密に量る．カプセルから内容物を適切な方法で除去し，個々の空のカプセルの質量を精密に量る．個々の試料の質量から対応する空のカプセルの質量を差し引いて，それぞれの試料の内容物の質量を求める．内容物の質量と定量法により求めた平均含量から，計算により個々の試料の含量推定値を求め，表示量に対する%で表す．判定値を計算する．

(iii) 軟カプセル剤：試料10個について，試料と質量の対応性に留意しながら，個々の質量をカプセルごと精密に量る．カプセルを切り開き，内容物を適当な溶媒で洗い出す．室温に約30分間放置し，残存している溶媒を蒸発させて除去する．このとき，カプセルが吸湿又は乾燥することを避けなければならない．個々の空カプセルの質量を精密に量り，個々の試料の質量から対応する空カプセルの質量を差し引いて，内容物の質量を求める．内容物の質量と定量法により求めた平均含量から，計算により個々の試料の含量推定値を求め，表示量に対する%で表す．判定値を計算する．

(iv) 錠剤とカプセル剤以外の固形製剤：「硬カプセル」の項に記載された方法と同様に個々の製剤を処理する．判定値を計算する．

(v) 液剤：試料10個について，内容液の質量又は容量と定量法により求めた平均含量から，計算により個々の試料の含量推定値を求め，表示量に対する%で表す．判定値を計算する．

2.1. 判定値の計算

「含量均一性試験」の項に従って判定値を計算する．ただし，◆$\bar{X}$はA◆に，また個々の試料の有効成分含量は下記に示した有効成分含量の推定値に置き換える．

x_1，x_2，…，x_n：試料1個に含まれる有効成分含量の推定値

$$x_i = w_i \times \frac{A}{\bar{W}}$$

w_1，w_2，…，w_n：試験した個々の試料の質量

A：適当な方法で測定して求めた有効成分含量(表示量に対する%)

$\bar{W}$：個々の質量(w_1，w_2，…，w_n)の平均値

3. 判定基準

別に規定するもののほか，次の判定基準を適用する．

(i) 固形製剤及び液剤：初めの試料10個について判定値を計算し，その値が$L1$%を超えないときは適合とする．もし判定値が$L1$%を超えるときは，更に残りの試料20個について同様に試験を行い，判定値を計算する．2回の試験を併せた30個の

試料の判定値が$L1$%を超えず，かつ個々の製剤の含量が，含量均一性試験又は質量偏差試験の「判定値の計算」の項で示した$(1-L2\times0.01)M$ 以上で，かつ$(1+L2\times0.01)M$ を超えるものがないときは適合とする．別に規定するもののほか，$L1$を15.0，$L2$を25.0とする．

表6.02−1 含量均一性試験及び質量偏差試験の各製剤への適用

剤形	タイプ	サブタイプ	含量／有効成分濃度 25mg以上かつ25%以上	含量／有効成分濃度 25mg未満又は25%未満
錠剤	素錠		MV	CU
	コーティング錠	フィルムコーティング錠	MV	CU
		その他	CU	CU
カプセル剤	硬カプセル		MV	CU
	軟カプセル	懸濁剤，乳化剤，ゲル	CU	CU
		液剤	MV	MV
個別容器に入った固形製剤◆(分包品，凍結乾燥製剤等)◆	単一組成		MV	MV
	混合物	最終容器内で溶液を凍結乾燥した製剤	MV	MV
		その他	CU	CU
個別容器に入った製剤◆(完全に溶解した液)◆			MV	MV
その他			CU	CU

CU：含量均一性試験，MV：質量偏差試験

表6.02−2

変数	定義	条件	値
$\bar{X}$	表示量に対する%で表した個々の含量の平均 $(x_1, x_2, \cdots, x_n)$		
$x_1, x_2, \cdots, x_n$	試験した個々の試料に含まれる有効成分含量(表示量に対する%)		
n	試料数(試験した試料の全個数)		
k	判定係数	試料数nが10のとき	2.4
		試料数nが30のとき	2.0
s	標準偏差		$\sqrt{\dfrac{\sum_{i=1}^{n}(x-\bar{X})^2}{n-1}}$
RSD	相対標準偏差(平均値に対し，%で表した標準偏差)		$\dfrac{100s}{\bar{X}}$
M(ケース1) $T\leqq101.5$の場合に適用	基準値	$98.5\%\leqq\bar{X}\leqq101.5\%$	$M=\bar{X}$ $(AV=ks)$
		$\bar{X}<98.5\%$	$M=98.5\%$ $(AV=98.5-\bar{X}+ks)$
		$\bar{X}>101.5\%$	$M=101.5\%$ $(AV=\bar{X}-101.5+ks)$
M(ケース2) $T>101.5$の場合に適用	基準値	$98.5\%\leqq\bar{X}\leqq T$	$M=\bar{X}$ $(AV=ks)$
		$X<98.5\%$	$M=98.5\%$ $(AV=98.5-\bar{X}+ks)$
		$\bar{X}>T$	$M=T\%$ $(AV=\bar{X}-T+ks)$
判定値(AV)			一般式：$\lvert M-X\rvert+ks$ (種々の場合の計算は上に示した)
$L1$	判定値の最大許容限度値		$L1=15.0$ 他に規定する場合を除く．
$L2$	個々の含量のMからの最大許容偏差	個々の含量の下限値は$0.75M$，上限値は$1.25M$ ($L2=25.0$とする)	$L2=25.0$ 他に規定する場合を除く．
T	目標含量．各条で別に規定する場合を除き，Tは100.0%とする．		

〈905〉 UNIFORMITY OF DOSAGE UNITS

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. Portions of the general chapter text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (✦ ✦) to specify this fact.

✦[NOTE—In this chapter, *unit* and *dosage unit* are synonymous.]✦

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or ✦*Weight Variation*✦ (see Table 1). The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for ✦*Weight Variation*✦ is applicable for the following dosage forms:

(W1)	Solutions enclosed in unit-dose containers and into soft capsules;
(W2)	solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
(W3)	solids (including sterile solids) that are packaged in single-unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4)	hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting *Content Uniformity* requirements.

The test for *Content Uniformity* is required for all dosage forms not meeting the above

conditions for the ✦*Weight Variation*✦ test. ✦Where compliance with the *Content Uniformity* test is required, then, by application of the provision for use of alternative methods provided in the *General Notices* section of this Pharmacopeia, it is possible for manufacturers to ensure this compliance by application of the *Weight Variation* test where the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%. This RSD determination may be based on the manufacturer's process validation and product development data. ✦The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*. ✦Where the *Weight Variation* test is used in this way, the product must, if tested, nevertheless comply with the official compendial test for *Content Uniformity*.✦

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers ✦and into soft capsules✦			WV	WV
Others			CU	CU

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the *Content Uniformity* test, it may be necessary to establish a correction factor to be applied to the results of the latter.

Solid Dosage Forms— Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see *Table 2*).

Liquid Dosage Forms— Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use, and express the results as delivered dose. Calculate the acceptance value (see *Table 2*).

Calculation of Acceptance Value— Calculate the acceptance value by the formula:

$$\left|M - \overline{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents ($\chi_1, \chi_2, \ldots, \chi_n$), expressed as a percentage of the label claim		
$\chi_1, \chi_2, \ldots, \chi_n$	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(\chi_i - \overline{X})^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\overline{X}$
M (case 1)	Reference value	If 98.5% $\leq\overline{X}$	

to be applied when T ≤101.5		≤101.5%, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >101.5%, then	M = 101.5% (AV = $\bar{X}$ – 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤$\bar{X}$ ≤T, then	M = $\bar{X}$ (AV = ks)
		If $\bar{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\bar{X}$ + ks)
		If $\bar{X}$ >T, then	M = T% (AV = $\bar{X}$ – T + ks)
Acceptance value (AV)			general formula: $\lvert M - \bar{X} \rvert + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than [1–(0.01)(L2)]M, while on the high side no dosage unit result can be greater than [1 + (0.01)(L2)]M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. For purposes of this Pharmacopeia, unless otherwise stated in the individual monograph, T is 100.0%, and for manufacturing purposes, T is the manufacturer's approved target test amount value at the time of manufacture.		

✦WEIGHT VARIATION✦

Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percent of label claim (see *Calculation of Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or Film-Coated Tablets— Accurately weigh 10 tablets individually. Calculate the content, expressed as % of label claim, of each tablet from the ✦weight✦ of the individual tablet and the result of the *Assay*. Calculate the acceptance value.

Hard Capsules— Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net ✦weight✦ of its contents by subtracting the ✦weight✦ of the shell from the respective gross ✦weight✦. Calculate the drug substance content of each capsule from the ✦net weight✦ of the individual capsule ✦content✦ and the result of the *Assay*. Calculate the acceptance value.

Soft Capsules— Accurately weigh 10 intact capsules individually to obtain their gross ✦weights✦, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content in each capsule from the ✦weight✦ of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Solid Dosage Forms Other Than Tablets and Capsules— Proceed as directed for *Hard Capsules,* treating each unit as described therein. Calculate the acceptance value.

Liquid Dosage Forms— Accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content in each container from the mass of product removed from the individual containers and the result of the assay. Calculate the acceptance value.

Calculation of Acceptance Value— Calculate the acceptance value as shown in

Content Uniformity, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$	=	individual estimated contents of the units tested, where $\chi_i = w_i \times A/\overline{W}$
$w_1, w_2, \ldots, w_n$	=	individual ✦weights✦ of the units tested
A	=	content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{W}$	=	mean of individual ✦weights✦ $(w_1, w_2, \ldots, w_n)$

CRITERIA

Apply the following criteria, unless otherwise specified.

Solid and Liquid Dosage Forms— The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%. If the acceptance value is > L1%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is ≤ L1%, and no individual content of ✦any✦ dosage unit is less than [1 − (0.01)(L2)]M nor more than [1 + (0.01)(L2)]M ✦as specified✦ in the *Calculation of Acceptance Value* under *Content Uniformity* or under ✦*Weight Variation.*✦ Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
General Chapter	William E. Brown Senior Scientific Liaison 1-301-816-8380	(GCDF2010) General Chapters - Dosage Forms

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2.9.40. UNIFORMITY OF DOSAGE UNITS

To ensure the consistency of dosage units, each unit in a batch should have an active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit. Unless otherwise stated, the uniformity of dosage units specification is not intended to apply to suspensions, emulsions or gels in single-dose containers intended for cutaneous administration. The test for content uniformity is not required for multivitamin and trace-element preparations.

The term 'uniformity of dosage unit' is defined as the degree of uniformity in the amount of the active substance among dosage units. Therefore, the requirements of this chapter apply to each active substance being comprised in dosage units containing one or more active substances, unless otherwise specified elsewere in this Pharmacopoeia.

The uniformity of dosage units can be demonstrated by either of 2 methods: content uniformity or mass variation (see Table 2.9.40.-1).

The test for content uniformity of preparations presented in dosage units is based on the assay of the individual contents of active substance(s) of a number of dosage units to determine whether the individual contents are within the limits set. The content uniformity method may be applied in all cases.

The test for mass variation is applicable for the following dosage forms:

(1) solutions enclosed in single-dose containers and in soft capsules;

(2) solids (including powders, granules and sterile solids) that are packaged in single-dose containers and contain no added active or inactive substances;

(3) solids (including sterile solids) that are packaged in single-dose containers, with or without added active or inactive substances, that have been prepared from true solutions and freeze-dried in the final containers and are labelled to indicate this method of preparation;

(4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of an active substance comprising 25 per cent or more, by mass, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other active substances present in lesser proportions is demonstrated by meeting content uniformity requirements.

The test for content uniformity is required for all dosage forms not meeting the above conditions for the mass variation test. Alternatively, products that do not meet the 25 mg/25 per cent threshold limit may be tested for uniformity of dosage units by mass variation instead of the content uniformity test on the following condition: the concentration Relative Standard Deviation (RSD) of the active substance in the final dosage units is not more than 2 per cent, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (*m/m* or *m/V*), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit mass. See the RSD formula in Table 2.9.40.-2.

CONTENT UNIFORMITY

Select not less than 30 units, and proceed as follows for the dosage form designated. Where different procedures are used for assay of the preparation and for the content uniformity test, it may be necessary to establish a correction factor to be applied to the results of the latter.

Solid dosage forms. Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see Table 2.9.40.-2).

Liquid dosage forms. Assay 10 units individually using an appropriate analytical method. Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use. Express the results as delivered dose. Calculate the acceptance value (see Table 2.9.40.-2).

Calculation of Acceptance Value

Calculate the Acceptance Value (*AV*) using the formula:

$$|M - \overline{X}| + ks$$

for which the terms are as defined in Table 2.9.40.-2.

Table 2.9.40.-1. – *Application of Content Unformity (CU) and Mass Variation (MV) test for dosage forms*

Dosage forms	Type	Sub-Type	Dose and ratio of active substance	
			≥ 25 mg and ≥ 25 per cent	< 25 mg or < 25 per cent
Tablets	uncoated		MV	CU
	coated	film-coated	MV	CU
		others	CU	CU
Capsules	hard		MV	CU
	soft	suspensions, emulsions, gels	CU	CU
		solutions	MV	MV
Solids in single-dose containers	single component		MV	MV
	multiple components	solution freeze-dried in final container	MV	MV
		others	CU	CU
Solutions enclosed in single-dose containers			MV	MV
Others			CU	CU

Table 2.9.40.-2.

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents (x_1, x_2,..., x_n), expressed as a percentage of the label claim		
$x_1, x_2, ..., x_n$	Individual contents of the dosage units tested, expressed as a percentage of the label claim		
n	Sample size (number of dosage units in a sample)		
k	Acceptability constant	If n = 10, then	2.4
		If n = 30, then	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(x_i - \overline{X})^2}{n-1}\right]^{1/2}$
RSD	Relative standard deviation		$\frac{100s}{\overline{X}}$
M (case 1) To be applied when $T \leq 101.5$	Reference value	If 98.5 per cent $\leq \overline{X} \leq$ 101.5 per cent, then	$M = \overline{X}$ ($AV = ks$)
		If $\overline{X}$ < 98.5 per cent, then	M = 98.5 per cent (AV = 98.5 $- \overline{X} + ks$)
		If $\overline{X}$ > 101.5 per cent, then	M = 101.5 per cent ($AV = \overline{X} - 101.5 + ks$)
M (case 2) To be applied when T > 101.5	Reference value	If 98.5 per cent $\leq \overline{X} \leq T$, then	$M = \overline{X}$ ($AV = ks$)
		If $\overline{X}$ < 98.5 per cent, then	M = 98.5 per cent (AV = 98.5 $- \overline{X} + ks$)
		If $\overline{X} > T$, then	$M = T$ per cent ($AV = \overline{X} - T + ks$)
Acceptance value (AV)			General formula: $\lvert M - \overline{X} \rvert + ks$ Calculations are specified above for the different cases.
$L1$	Maximum allowed acceptance value		$L1$ = 15.0 unless otherwise specified
$L2$	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than 0.75 M while on the high side, no dosage unit result can be greater than 1.25 M (This is based on $L2$ value of 25.0)	$L2$ = 25.0 unless otherwise specified
T	Target content per dosage unit at time of manufacture, expressed as a percentage of the label claim. T is equal to 100 per cent unless an overage for stability reasons has been approved, in which case it is greater than 100 per cent		

MASS VARIATION

Carry out an assay for the active substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percentage of label claim (see Calculation of Acceptance Value). Assume that the concentration (mass of active substance per mass of dosage unit) is uniform. Select not less than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or film-coated tablets. Accurately weigh 10 tablets individually. Calculate the active substance content, expressed as percentage of label claim, of each tablet from the mass of the individual tablets and the result of the assay. Calculate the acceptance value.

Hard capsules. Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by suitable means. Accurately weigh the emptied shells individually, and calculate for each

capsule the net mass of its contents by subtracting the mass of the shell from the respective gross mass. Calculate the active substance content in each capsule from the mass of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Soft capsules. Accurately weigh 10 intact capsules individually to obtain their gross masses, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 min, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the active substance content on each capsule from the mass of product removed from the individual capsules and the result of the assay. Calculate the acceptance value.

Solid dosage forms other than tablets and capsules. Proceed as directed for hard capsules, treating each unit as described therein. Calculate the acceptance value.

Liquid dosage forms. Accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the active substance content in each container from the mass of product removed from the individual containers and the result of the assay. Calculate the acceptance value.

Calculation of Acceptance Value. Calculate the acceptance value (*AV*) as shown in content uniformity, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$x_1, x_2, \ldots, x_n$ = individual estimated contents of the dosage units tested;

where

$$x_i = w_i \times \frac{A}{\overline{W}}$$

$w_1, w_2, \ldots, w_n$ = individual masses of the dosage units tested;

A = content of active substance (percentage of label claim) obtained using an appropriate analytical method (assay);

$\overline{W}$ = mean of individual masses of the units used in the assay.

CRITERIA

Apply the following criteria, unless otherwise specified.

Solid and liquid dosage forms. The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to $L1$. If the acceptance value is greater than $L1$, test the next 20 dosage units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to $L1$ and no individual content of the dosage unit is less than $(1 - L2 \times 0.01)M$ or more than $(1 + L2 \times 0.01)M$ in calculation of acceptance value under content uniformity or under mass variation. Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

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corrected 6.1

2.9.43. APPARENT DISSOLUTION

This method is mainly used to determine the apparent dissolution rate of pure solid substances. It may also be used for the determination of the apparent dissolution rate of active substances in preparations presented as powders or granules.

APPARATUS

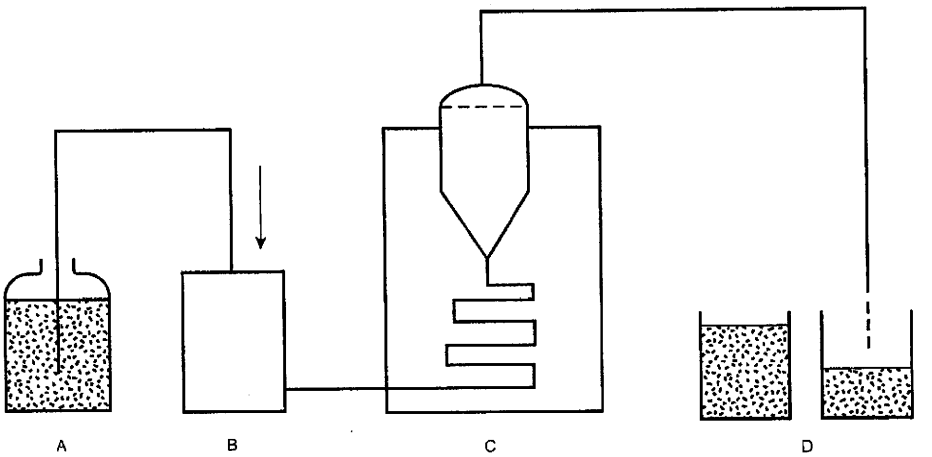
All parts of the apparatus that may come into contact with the sample or the dissolution medium are chemically inert and do not adsorb, react with, or interfere with the test sample. No part of the assembly or its environment contributes significant motion, agitation or vibration beyond that resulting from the flow-through system.

Apparatus that permits observation of the sample is preferable.

The apparatus (see Figure 2.9.43.-1) consists of:

- a reservoir for the dissolution medium;
- a pump that forces the dissolution medium upwards through the flow-through cell;
- a flow-through cell, preferably of transparent material, mounted vertically with a filter system preventing escape of undissolved particles;
- a water-bath that will maintain the dissolution medium at the chosen temperature (generally 37 ± 0.5 °C).

The flow-through cell shown in Figure 2.9.43.-2 consists of 3 parts that fit into each other. The lower part supports a system of grids and filters on which the powder is placed. The middle part, which fits onto the lower part, contains an



A. reservoir for dissolution medium B. pump C. thermostatically controlled flow-through cell and filter D. collecting vessels for analysis

Figure 2.9.43.-1. – *Flow-through apparatus*

る．更に微粒子試験用水30mLずつで3回繰り返す．引き続きメンブランフィルター上から水がなくなるまで穏やかに吸引した後，メンブランフィルターを取り，ペトリ皿に入れ，ふたをずらして50℃以下で乾燥する．乾燥後，ペトリ皿を顕微鏡のステージに置き，前記と同様に顕微鏡を操作し，有効ろ過面上の300μm以上の不溶性微粒子数を測定する．不溶性微粒子の大きさは最長径とする．

3.2. 用時溶解して用いる点眼剤

操作は水性点眼剤に準じて行う．ただし，添付された溶解液に溶解した後，試料量は25mLとする．

3.3. 懸濁性点眼剤

操作は水性点眼剤に準じて行う．ただし，あらかじめ微粒子試験用水で洗浄した容器に試料25mLを量り，懸濁溶解用液又は適当な溶解用溶媒を適当量加えて，振り混ぜて懸濁粒子を溶解し，試料溶液として試験を行う．

なお，溶媒を用いる場合には，使用する溶媒に耐えるメンブランフィルターを使用する．

3.4. 1回量包装点眼剤

操作は水性点眼剤に準じて行う．ただし，試料は10本を用いる．また，メンブランフィルターは直径13mm，微粒子捕集口径4mmのフィルターホルダーを用いる．

4. 判定

本剤1mL中の個数に換算するとき，300μm以上の不溶性微粒子が1個以下であるときは適合とする．

6.09 崩壊試験法

本試験法は，三薬局方での調和合意に基づき規定した試験法である．

なお，三薬局方で調和されていない部分は「◆ ◆」で囲むことにより示す．

崩壊試験法は，錠剤，カプセル剤，◆顆粒剤，シロップ用剤，丸剤◆が試験液中，定められた条件で規定時間内に崩壊するかどうかを確認する試験法である．崩壊試験法は，製剤中の有効成分が完全に溶解するかどうかを確認することを目的としていない．

1. 装置

装置は，高さ138～160mmで浸漬部の内径が97～115mmの1000mL低形ビーカー，37±2℃で温度調節可能な恒温槽，1分間29～32往復，振幅53～57mmで上下する試験器及び電動機からなっている．ビーカーに入れる試験液の量は，試験器が最も上がったとき，試験器の網面が液面から下へ少なくとも15mm以上離れるようにし，試験器が最も下がったとき，網面はビーカーの底から25mm以上で，試験器が完全に沈むことがあってはならない．電動機の上方及び下方への移動時間は等しくし，また上下の方向転換は，急ではなく滑らかに行われるようにする．試験器は垂直軸に沿って動作するようにし，水平方向に軸が動いたり移動したりしないようにする．

（i） 試験器：試験器には，長さ77.5±2.5mm，内径20.7～23mm，厚さ1.0～2.8mmの両端が開口した透明な管6本と，これらの管を上下方向からはさみ垂直に立てておくための直径88～92mm，厚さ5～8.5mmの2枚のプラスチック板があり，これらの板には，それぞれ直径22～26mmの穴が6個，中心から等距離かつ等間隔で開いている．下のプラスチック板の下面には，網目の開き1.8～2.2mm，線径0.57～0.66mmの平らなステンレス網を取り付ける．試験器は，2枚のプラスチック板を貫く3本の支柱を用いて，組み立て固定する．試験器は図6.09－1に示した構造に合うものである．ガラス管と網が規格に合っている限り，他の部分の多少の変更は可能で，◆例えば，ガラス管を試験器に固定するため，上のプラスチック板の上面及び下のプラスチック板の下面に，それぞれの穴に当たる部分に直径22～26mmの穴を6個開けた直径88～92mm，厚さ0.5～1mmの耐酸性の金属板を取り付けてもよい．◆ 試験器はその中心軸に沿って上下運動できるように，電動機に適当な方法で吊るす．

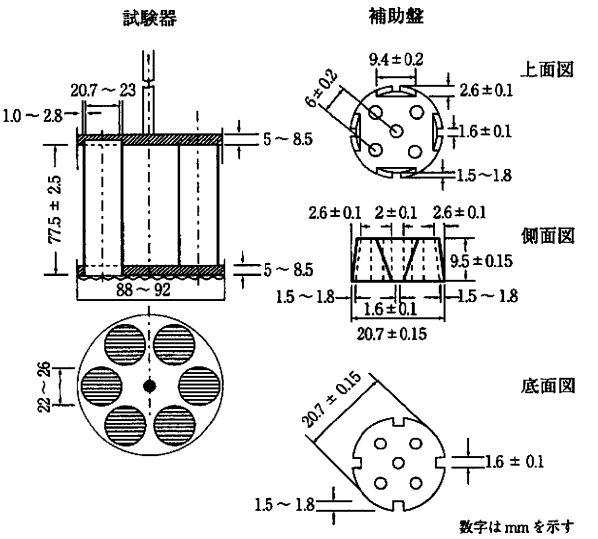
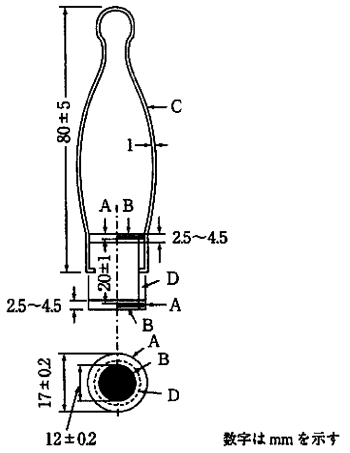


図6.09－1 崩壊試験装置

（ii） 補助盤：補助盤は，各条にその使用が規定されている場合にのみ，各ガラス管に入れて使用できる．補助盤は，高さ9.5±0.15mm，直径20.7±0.15mmの円柱状で，比重1.18～1.20の透明なプラスチックからなる．補助盤には，盤の上下を垂直に貫く直径2±0.1mmの孔が五つ平行に開いており，一つは補助盤の中心に，他の四つは中心から6±0.2mmの距離にそれぞれ等間隔に開いている．補助盤の側面には，盤面とほぼ直角に，同一の台形状の切り込みが4つ等間隔にある．台形は対称形で，上下の平行線は，中心軸から6mmにある隣接した2つの孔を結ぶ線と平行に位置している．台形の平行線の下線部は長さ1.6±0.1mmで円周部から深さ1.5～1.8mmの位置にあり，上線部は長さ9.4±0.2mmで深さ2.6±0.1mmの位置にある．補助盤は図6.09－1の規格に適合するもので，表面はすべて滑らかである．補助盤の使用が規定されている場合は，それぞれのガラス管に1個の補助盤を入れ，操作法に従い試験する．なお，崩壊を自動的に検出する目的で，加工した特殊な補助盤を用いる場合，その補助盤の比重，サイズは規格に適合するものでなければならない．また，それが使用できるのは各条で規定されている場合に限られる．

◆（iii） 補助筒：補助筒は図6.09－2に示すように内径12±0.2mm，外径17±0.2mm，長さ20±1mmのプラスチック筒Dの両端外側にねじを切り，内径12±0.2mm，外径17±0.2mm，長さ2.5～4.5mmのプラスチック筒Aの内側にねじを切り，網

目の開き0.42mm，線径0.29mmの耐酸性の網を置いて，先の円筒の両端に密着させたものである．補助筒の上下の網の間隔は20±1mmとし，外側中央部に直径1mmの耐酸性針金を用いて高さ80±5mmの取手を付ける．補助筒は，顆粒剤及び腸溶顆粒を充てんしたカプセル剤を試験するときに用いる．◆



A及びD：プラスチック筒
B：網目の開き0.42mm，線径0.29mmの耐酸性の網
C：耐酸性針金の取手

◆図6.09－2 補助筒◆

2. 操作法

2.1. 即放性製剤

錠剤，カプセル剤，◆丸剤(生薬を含む丸剤を除く)◆については，試験器の6本のガラス管にそれぞれに試料1個ずつを入れ，補助盤の使用が規定されている場合は補助盤を入れ，◆別に規定するもののほか，試験液に水を用いて，◆37±2℃で試験器を作動させる．◆別に規定するもののほか，素錠は30分後，コーティング錠及び丸剤は60分後，カプセル剤は20分後，◆試験器を試験液から引き上げ，試料の崩壊の様子を観察する．◆試料の残留物をガラス管内に全く認めないか，又は認めても明らかに原形をとどめない軟質の物質であるとき，あるいは不溶性の剤皮又はカプセル皮膜の断片であるとき，試料は崩壊したものとする．◆ すべての試料が崩壊した場合，適合とする．1個又は2個が崩壊しなかった場合，更に12個の試料について試験を行い，計18個の試料うち16個以上の試料が崩壊した場合，適合とする．◆生薬を含む丸剤については，試験液に崩壊試験第1液を用いて同様に，60分間，試験を行う．試料の残留物をガラス管内に認めるときは，引き続き崩壊試験第2液で60分間，試験を行う．◆

◆顆粒剤及びシロップ用剤については，30号ふるい(500μm)を用いて製剤の粒度の試験法〈6.03〉に準じてふるい，30号ふるいに残留するもの0.10gずつをそれぞれ補助筒6個にとり，補助筒を試験器のガラス管に1個ずつ入れて固定し，別に規定するもののほか，試験液に水を用いて，37±2℃で試験器を作動させる．別に規定するもののほか，剤皮を施していない顆粒は30分後，剤皮を施した顆粒は60分後，試験器を試験液から引き上げ，補助筒を取り出して試料の崩壊の様子を観察する．試料の残留物を補助筒内に全く認めないか，又は認めても明らかに原形をとどめない軟質の物質であるとき，あるいは剤皮の断片であるとき，崩壊したものとする．すべての補助筒内の試料が崩壊した場合，適合とする．1個又は2個の補助筒内の試料が崩壊しなかった場合，更に12個の試料について試験を行い，計18個の試料のうち16個以上の試料が完全に崩壊した場合，適合とする．◆

◆2.2. 腸溶性製剤

別に規定するもののほか，崩壊試験第1液及び崩壊試験第2液による2つの試験を別々に行う．

2.2.1. 腸溶錠及び腸溶性カプセル剤

(i) 崩壊試験第1液による試験：試験液に崩壊試験第1液を用いて120分間，即放性製剤の操作法に従って試験を行う．腸溶錠及び腸溶性カプセル剤が壊れた場合，又は腸溶性皮膜が開口，破損した場合，崩壊したものとする．すべての試料が崩壊しない場合，適合とする．1個又は2個が崩壊した場合は，更に12個の試料について試験を行い，計18個の試料のうち16個以上の試料が崩壊しない場合，適合とする．

(ii) 崩壊試験第2液による試験：試験液に崩壊試験第2液を用いて60分間，即放性製剤の操作法に従って試験を行い，崩壊の適否を判定する．

2.2.2. 腸溶顆粒剤及び腸溶顆粒を充てんしたカプセル剤

顆粒剤又はカプセル剤中より取り出した内容物を30号ふるい(500μm)を用いて製剤の粒度の試験法〈6.03〉に準じてふるい，30号ふるいに残留するもの0.10gずつをそれぞれ補助筒6個にとり，補助筒を試験器のガラス管に1個ずつ入れて固定し，次の試験を行う．

(i) 崩壊試験第1液による試験：試験液に崩壊試験第1液を用いて60分間，即放性製剤の操作法に従って試験を行う．試験器の網目から落ちる顆粒数が15粒以内のとき，適合とする．

(ii) 崩壊試験第2液による試験：試験液に崩壊試験第2液を用いて30分間，即放性製剤の操作法に従って試験を行い，崩壊の適否を判定する．◆

6.10 溶出試験法

本試験法は，三薬局方での調和合意に基づき規定した試験法である．

なお，三薬局方で調和されていない部分は「◆ ◆」で囲むことにより示す．

本試験は，経口製剤について溶出試験規格に適合しているかどうかを判定するために行うものであるが，◆併せて著しい生物学的非同等を防ぐことを目的としている．◆ 本試験における試料とは，最小投与量に相当するもので，錠剤では1錠，カプセルでは1カプセル，その他の製剤では規定された量を意味する．

1. 装置

1.1. 回転バスケット法の装置 (装置1)

装置は，ふたができるガラス又は透明で化学的に不活性な材質[1]の容器，モーター，回転軸及び円筒形のバスケットからなる．容器は，適当な大きさの恒温水槽に設置するか又は恒温ジャケットなどに入れ，加温する．恒温水槽又は恒温ジャケットは，試験中の容器内温度が37±0.5℃となるように，また，恒温水槽内の液体が滑らかに動くように調整する．攪拌部の滑らかな回転以外には，装置が設置された周辺環境や装置に起因する揺動や振動が生じないようにする．試験中は，試料及び攪拌

〈701〉 DISINTEGRATION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.* The texts of these pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present general chapter. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national *USP* text, and therefore not part of the harmonized text, are marked with symbols (✦ ✦) to specify this fact.

This test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. ✦Compliance with the limits on *Disintegration* stated in the individual monographs is required except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as extended-release dosage forms or delayed-release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.✦

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly— The basket-rack assembly consists of six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plates, each 88 to 92 mm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained. The basket-rack assembly conforms to the dimensions found in *Figure 1*.

Disks— The use of disks is permitted only where specified or allowed ✦in the monograph. If specified in the individual monograph, ✦ each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2 ± 0.1-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 ± 0.2 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 ± 0.1 mm, and its bottom edges lie at a depth of 1.5 to 1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified ✦in the individual monograph✦, add a disk to each tube, and operate the apparatus as directed under *Procedure*. The disks conform to dimensions found in *Figure 1*[1].