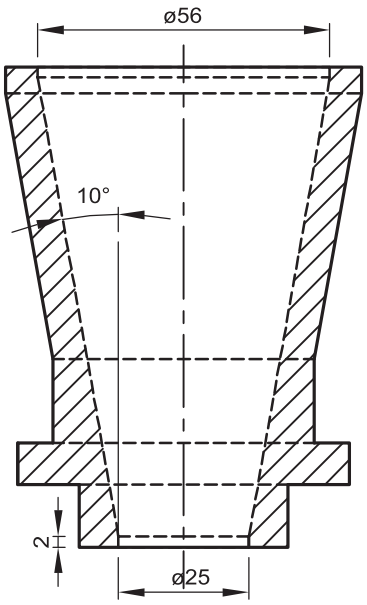

Figure 2.9.25.-2 – *Funnel*
(dimensions in millimetres)

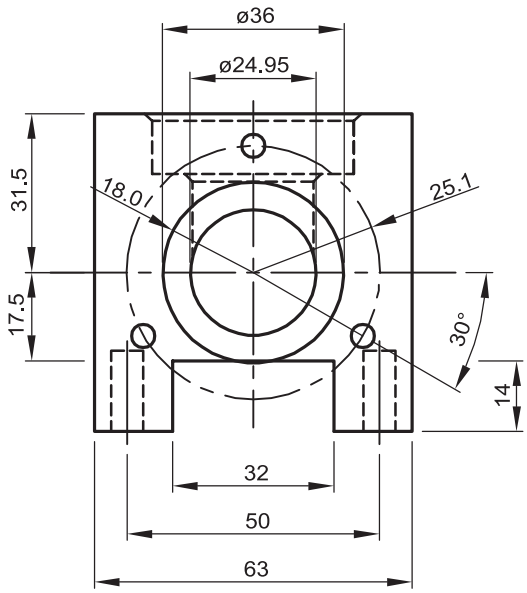

Figure 2.9.25.-3 – *Guide (section G-G)*
(dimensions in millimetres)

The gum is artificially chewed by the horizontal pistons, and the vertical piston ensures that the gum stays in the right place between chews.

Machine speed is controlled to ensure a constant cycle. One cycle (chew) is defined as follows: the horizontal pistons start from their outermost position, move to their innermost position and back to their outermost position. Within one cycle, the vertical piston moves from its lowest position to its uppermost position and back to its lowest position.

Each horizontal piston has a stroke of 25.0 mm. The maximum distance between these 2 pistons is 50 mm. The minimum distance between the 2 horizontal pistons is 0.1 mm to 1.0 mm. The vertical piston has a stroke of 22.0 mm.

Horizontal piston movement is controlled, so that the 2 pistons are at their innermost position at the same time. Vertical piston movement is controlled, so it does not conflict with the movement of the horizontal pistons.

If necessary, the machine can be constructed so that the horizontal pistons rotate around their own axes in opposite direction to each other by the end of the chew in order to obtain maximum chewing.

All parts of the apparatus that may come in contact with the preparation or the dissolution medium are chemically inert and do not adsorb, react or interfere with the sample.

PROCEDURE

For each determination, the following information is needed:

- composition, volume and temperature of the dissolution medium,
- number of chews per minute,
- time and sampling method,
- whether the analysis is performed on the gum residue or on the dissolution medium,
- method of analysis.

Place the prescribed volume of dissolution medium in the chewing chamber, usually 20 ml of *phosphate buffer solution pH 6.0 R2*. Maintain the medium temperature at 37 ± 0.5 °C using an electrical device with external control. Set the piston speed at the prescribed number of chews per minute (usually 60). Accurately weigh a portion of gum or the whole gum, put it into the chewing chamber and start the machine.

SAMPLING AND EVALUATION

Stop the apparatus at the prescribed time. Remove the gum residue and take a sample of the dissolution medium. Determine the content of active substance(s) by a suitable method. Medium replacement may be made after each sampling procedure; compensation by calculation of medium volume change or sample dilution is needed. Alternatively, determine the content of active substance(s) remaining in the gum residue. Carry out the test successively on 6 medicated chewing gums.

The quantity of active substance(s) dissolved in a specified time is expressed as a percentage of the content stated on the label.

07/2005:20940

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. 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 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 active or inactive added substances;

(3) solids (including sterile solids) that are packaged in single-dose 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 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:

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

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

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.

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		$\left[\frac{\sum_{i=1}^{n}(x_1-\overline{X})^2}{n-1}\right]^{1/2}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$\frac{100s}{\overline{X}}$
M (case 1) To be applied when $T \leq 101.5$	Reference value	If 98.5 per cent ≤ $\overline{X}$ ≤ 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 ≤ $\overline{X} \leq T$, 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 test sample amount at time of manufacture		

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.

$x_1, x_2, ..., x_n$ = individual estimated contents of the dosage units tested,

where

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

$w_1, w_2, ..., w_n$ = individual masses of the dosage units tested,

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

$\overline{W}$ = mean of individual masses ($w_1, w_2, ..., w_n$).

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 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 $(1 - L2 \times 0.01)M$ nor 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.