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.

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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:

\[ M - \bar{X} + k \times s \]

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 means of a suitable method. 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 Uniformity (CU) and Mass Variation (MV) test for dosage forms

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Type</th>
<th>Sub-Type</th>
<th>Dose and ratio of active substance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥ 25 mg and ≥ 25 per cent</td>
</tr>
<tr>
<td>Tablets</td>
<td>uncoated</td>
<td>MV</td>
<td>CU</td>
</tr>
<tr>
<td></td>
<td>coated</td>
<td>MV</td>
<td>CU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>others</td>
<td>CU</td>
</tr>
<tr>
<td>Capsules</td>
<td>hard</td>
<td>MV</td>
<td>CU</td>
</tr>
<tr>
<td></td>
<td>soft</td>
<td>suspensions, emulsions, gels</td>
<td>CU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>solutions</td>
<td>MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MV</td>
</tr>
<tr>
<td>Solids in single-dose containers</td>
<td>single component</td>
<td>MV</td>
<td>MV</td>
</tr>
<tr>
<td></td>
<td>multiple components</td>
<td>solution freeze-dried in final container</td>
<td>MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>others</td>
</tr>
<tr>
<td>Solutions enclosed in single-dose containers</td>
<td></td>
<td>MV</td>
<td>MV</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>CU</td>
</tr>
</tbody>
</table>
Table 2.9.40.-2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Conditions</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\bar{x}$</td>
<td>Mean of individual contents ($x_1, x_2, \ldots, x_n$), expressed as a percentage of the label claim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$x_1, x_2, \ldots, x_n$</td>
<td>Individual contents of the dosage units tested, expressed as a percentage of the label claim</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>Sample size (number of dosage units in a sample)</td>
<td>If $n = 10$, then</td>
<td>$2.4$</td>
</tr>
<tr>
<td>$k$</td>
<td>Acceptability constant</td>
<td>If $n = 30$, then</td>
<td>$2.0$</td>
</tr>
<tr>
<td>$s$</td>
<td>Sample standard deviation</td>
<td></td>
<td>$\sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n-1}}$</td>
</tr>
<tr>
<td>RSD</td>
<td>Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)</td>
<td></td>
<td>$\frac{100 \times s}{\bar{x}}$</td>
</tr>
<tr>
<td>$M$ (case 1)</td>
<td>Reference value</td>
<td>If $98.5$ per cent $\leq \bar{x} \leq 101.5$ per cent, then</td>
<td>$M = \bar{x}$  \hspace{1cm} (AV = $k$s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If $\bar{x} &lt; 98.5$ per cent, then</td>
<td>$M = 98.5$ per cent  \hspace{1cm} (AV = $98.5 - \bar{x} + ks$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If $\bar{x} &gt; 101.5$ per cent, then</td>
<td>$M = 101.5$ per cent \hspace{1cm} (AV = $\bar{x} - 101.5 + ks$)</td>
</tr>
<tr>
<td>$M$ (case 2)</td>
<td>Reference value</td>
<td>If $98.5$ per cent $\leq \bar{x} \leq T$, then</td>
<td>$M = \bar{x}$  \hspace{1cm} (AV = $k$s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If $\bar{x} &lt; 98.5$ per cent, then</td>
<td>$M = 98.5$ per cent \hspace{1cm} (AV = $98.5 - \bar{x} + ks$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If $\bar{x} &gt; T$, then</td>
<td>$M = T$ per cent \hspace{1cm} (AV = $\bar{x} - T + ks$)</td>
</tr>
<tr>
<td>Acceptance value (AV)</td>
<td>General formula:</td>
<td></td>
<td>$M = \bar{x} - k$s</td>
</tr>
<tr>
<td>$L_1$</td>
<td>Maximum allowed acceptance value</td>
<td></td>
<td>$L_1 = 15.0$ unless otherwise specified</td>
</tr>
<tr>
<td>$L_2$</td>
<td>Maximum allowed range for deviation of each dosage unit tested from the calculated value of $M$</td>
<td>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 $L_2$ value of 25.0)</td>
<td>$L_2 = 25.0$ unless otherwise specified</td>
</tr>
<tr>
<td>$T$</td>
<td>Target test sample amount at time of manufacture</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.9.40. Uniformity of dosage units

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.

\[ x_1, x_2, ..., x_n = \text{individual estimated contents of the dosage units tested}, \]

where

\[ x_i = w_i \times \frac{A}{W} \]

\[ w_1, w_2, ..., w_n = \text{individual masses of the dosage units tested}, \]

\[ A = \text{content of active substance (percentage of label claim) obtained using an appropriate analytical method}, \]

\[ W = \text{mean of individual masses (} w_1, w_2, ..., w_n) \]

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.