Method. Pour 5 ml of water at 36.5 ± 0.5 °C into the inner tube (A), introduce a suppository with the tip downwards and onto that, place the inset (C1 or C2). Note the time which elapses between this moment and the moment when the lower, rimmed end of the glass rod (C1) or the steel rod (C2) reaches the narrowed part of the inner glass tube. Melting or dissolution is then considered as complete.

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2.9.23. PYCNOMETRIC DENSITY OF SOLIDS

The test for pycnometric density of solids is intended to determine the volume occupied by a known mass of powder by measuring the volume of gas displaced under defined conditions. Hence, its pycnometric density is calculated.

APPARATUS

The apparatus (see Figure 2.9.23.-1) consists of the following:
— a sealed test cell, with an empty cell volume (V_c), connected through a valve to a reference cell, with a reference volume (V_r),
— a system capable of pressurising the test cell with the measurement gas until a defined pressure (P) indicated by a manometer,
— the system is connected to a source of measurement gas, which is preferably helium, unless another gas is specified[5].
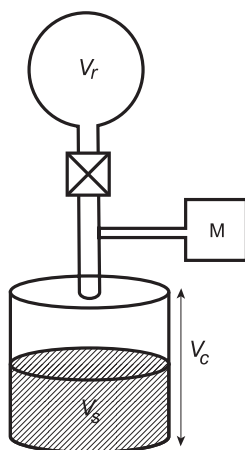
V_r	=	reference volume
V_c	=	cell volume
V_s	=	sample volume
M	=	manometer

Figure 2.9.23.-1. − *Schematic diagram of a gas pycnometer*

The temperature of the gas pycnometer is between 15 °C and 30 °C and must not vary by more than 2 °C during the course of measurement.

The apparatus is calibrated which means that the volumes (V_c) and (V_r) are determined, using calibrated, polished steel balls having a total volume (around 6 cm³) known to the nearest 0.001 cm³. The procedure described below is followed in two runs. Firstly, with an empty test cell and secondly with the steel balls placed in the test cell. The volumes (V_c) and (V_r) are calculated using the equation for the sample volume taking into account that the volume is zero in the first run.

METHOD

Weigh the test cell of the pycnometer and record the mass. Fill the test cell with a given mass of powder of the substance to be examined. Seal the test cell in the pycnometer. Remove volatile contaminants in the powder by degassing the powder under a constant purge of gas; occasionally, powders may initially have to be degassed under vacuum. Record the system reference pressure (P_r) as indicated by the manometer while the valve that connects the reference cell with the test cell is open. Close the valve to separate the reference cell from the test cell. Pressurise the test cell with the gas to an initial pressure (P_i) and record the value obtained. Open the valve to connect the reference cell with the test cell. Record the final pressure (P_f). Repeat the measurement sequence for the same powder sample until consecutive measurements of the sample volume (V_s) agree to within 0.5 per cent. The sample volume is expressed in cubic centimetres. Unload the test cell and measure the final powder mass (m) expressed in grams.

EXPRESSION OF THE RESULTS

The sample volume (V_s) is given by the expression:

$$V_s = V_c - \frac{V_r}{\dfrac{P_i - P_r}{P_f - P_r} - 1}$$

The density (ρ) is given by the equation:

$$\rho = \frac{m}{V_s}$$

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2.9.25. DISSOLUTION TEST FOR MEDICATED CHEWING GUMS

PRINCIPLE

The test is used to determine the dissolution rate of active substances in medicated chewing gums. This is done by applying a mechanical kneading procedure to a piece of gum placed in a small chamber designed to simulate the process of chewing.

APPARATUS

The chewing apparatus (Figure 2.9.25.-1) consists of:
— 1 chewing chamber,
— 1 vertical piston,
— 2 horizontal pistons with O-rings and sealing rings.

The chewing chamber consists of 4 individual parts:
— 1 central chamber,
— 1 funnel (Figure 2.9.25.-2),
— 2 guides with bushes (Figure 2.9.25.-3).

Funnel and guides are mounted on the central chamber. The O-rings are incorporated in the piston recess with the sealing ring round it; the sealing rings ensure that the chamber is watertight. The horizontal pistons are placed in the chewing chamber through the guides.

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

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(5) If gases other than helium are used, it would not be surprising to obtain values different from those obtained with helium, since the penetration of the gas is dependent on the size of the pore as well as the cross-sectional area of the penetrating molecule. For example, the pycnometric density of porous materials will be overestimated by a measure using nitrogen by comparison with helium.
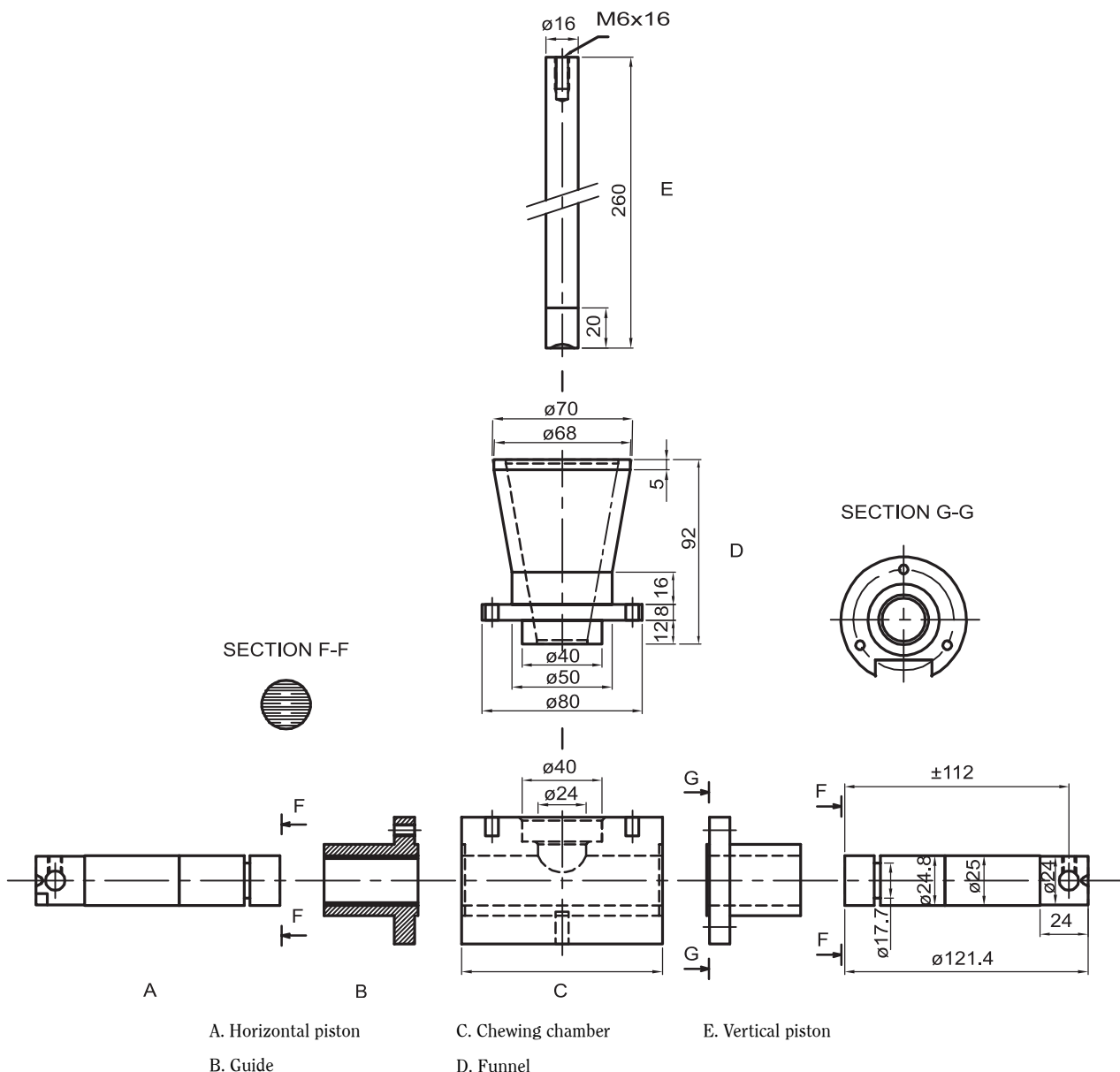
A. Horizontal piston
B. Guide
C. Chewing chamber
D. Funnel
E. Vertical piston

Figure 2.9.25.-1 − *Chewing chamber and pistons*
(dimensions in millimetres)

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.
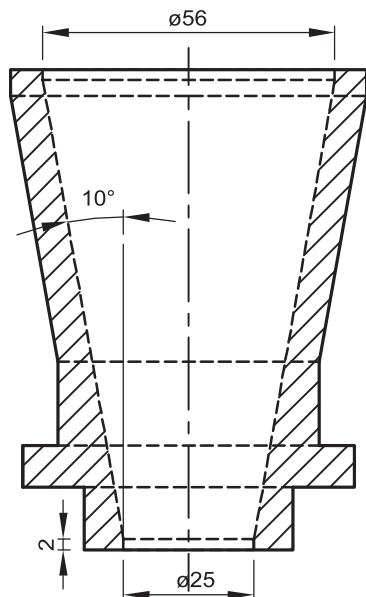

Figure 2.9.25.-2 − *Funnel*
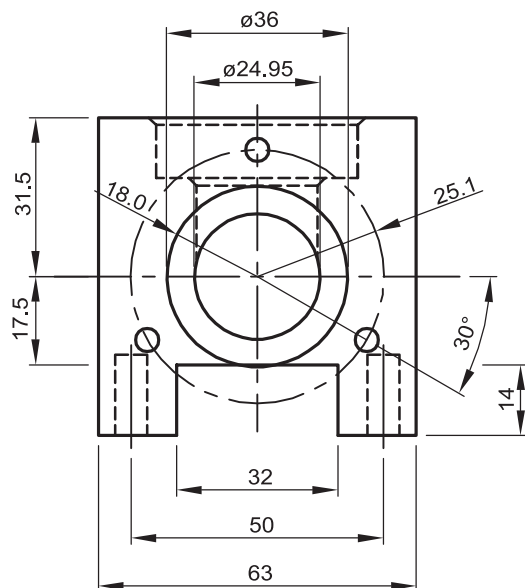(dimensions in millimetres)

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

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2.9.26. SPECIFIC SURFACE AREA BY GAS ADSORPTION

INTRODUCTION

The specific surface area of a powder is determined by physical adsorption of a gas on the surface of the solid and by calculating the amount of adsorbate gas corresponding to a monomolecular layer on the surface. Physical adsorption results from relatively weak forces (van der Waals forces)

between the adsorbate gas molecules and the adsorbent surface of the test powder. The determination is usually carried out at the temperature of liquid nitrogen. The amount of gas adsorbed can be measured by a volumetric or continuous flow procedure.

BRUNAUER, EMMETT AND TELLER (BET) THEORY AND SPECIFIC SURFACE AREA DETERMINATION

MULTI-POINT MEASUREMENT

The data are treated according to the Brunauer, Emmett and Teller (BET) adsorption isotherm equation:

$$\frac{1}{\left[V_a\left(\frac{P_o}{P}-1\right)\right]} = \frac{C-1}{V_m C} \times \frac{P}{P_o} + \frac{1}{V_m C} \tag{1}$$

P = partial vapour pressure of adsorbate gas in equilibrium with the surface at 77.4 K (b.p. of liquid nitrogen), in pascals,

P_o = saturated pressure of adsorbate gas, in pascals,

V_a = volume of gas adsorbed at standard temperature and pressure (STP) [273.15 K and atmospheric pressure (1.013×10^5 Pa)], in millilitres,

V_m = volume of gas adsorbed at STP to produce an apparent monolayer on the sample surface, in millilitres,

C = dimensionless constant that is related to the enthalpy of adsorption of the adsorbate gas on the powder sample.

A value of V_a is measured at each of not less than 3 values of P/P_o.

Then the BET value

$$\frac{1}{\left[V_a\left(\frac{P_o}{P}-1\right)\right]}$$

is plotted against P/P_o according to equation (1). This plot should yield a straight line usually in the approximate relative pressure range 0.05 to 0.3. The data are considered acceptable if the correlation coefficient, r, of the linear regression is not less than 0.9975; that is, r^2 is not less than 0.995. From the resulting linear plot, the slope, which is equal to $(C-1)/V_m C$, and the intercept, which is equal to $1/V_m C$, are evaluated by linear regression analysis. From these values, V_m is calculated as $1/(slope + intercept)$, while C is calculated as $(slope/intercept) + 1$. From the value of V_m so determined, the specific surface area, S, in $m^2 \cdot g^{-1}$, is calculated by the equation:

$$S = \frac{V_m N a}{m \times 22400} \tag{2}$$

N = Avogadro constant (6.022×10^{23} mol^{-1}),

a = effective cross-sectional area of one adsorbate molecule, in square metres (0.162 nm^2 for nitrogen and 0.195 nm^2 for krypton),

m = mass of test powder, in grams,

22400 = volume occupied by 1 mole of the adsorbate gas at STP allowing for minor departures from the ideal, in millilitres.

A minimum of 3 data points is required. Additional measurements may be carried out, especially when non-linearity is obtained at a P/P_o value close to 0.3.