Compliance with general chapter *2.9.40. Uniformity of dosage units* can be demonstrated by the following procedure, when large samples (sample size $n \geq 100$) are evaluated.

Application of this chapter does not constitute a mandatory requirement. It presents 2 alternative tests (Alternative 1 and Alternative 2). Fulfilling the requirements of either of the 2 alternatives is considered as evidence that the medicinal product tested complies with general chapter *2.9.40*. The 2 alternatives are considered equivalent in their demonstration of compliance with general chapter *2.9.40*.

ALTERNATIVE 1 (PARAMETRIC)

Select not fewer than 100 units according to a predefined sampling plan.

The consistency of dosage units is evaluated by content uniformity or mass variation as prescribed in Table 2.9.40.-1. Calculate the acceptance value (*AV*) using the following expression:

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

for which the terms are defined in Table 2.9.40.-2, but using the sample size-dependent value for *k* defined in Table 2.9.47.-1.

CRITERIA

Apply the following criteria, unless otherwise specified.

The requirements for dosage form uniformity are met if:

1. the acceptance value (*AV*) is less than or equal to $L1$; and
2. in the calculation of acceptance value (*AV*) under content uniformity or under mass variation, the number of individual dosage units outside $(1 \pm L2 \times 0.01)M$ is less than or equal to $c2$ as defined for a given sample size *n* in Table 2.9.47.-1.

Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

Table 2.9.47.-1. is to be interpreted as follows:

- for a sample size of $n = 400$, enter the table at $n \geq 385$: $k = 2.23$ and $c2 = 3$;
- for a sample size of $n = 450$, enter the table at $n \geq 407$: $k = 2.24$ and $c2 = 3$;
- for a sample size of $n = 500$, enter the table at $n \geq 490$: $k = 2.24$ and $c2 = 4$.

ALTERNATIVE 2 (NON-PARAMETRIC)

Select not fewer than 100 units according to a predefined sampling plan.

The consistency of dosage units is evaluated by content uniformity or mass variation as prescribed in Table 2.9.40.-1. Assay individually or weigh the units and calculate individual contents as prescribed in general chapter *2.9.40*. Count the number of individual dosage units with a content outside $(1 \pm L1 \times 0.01)T$ and the number of individual dosage units with a content outside $(1 \pm L2 \times 0.01)T$. Evaluate if the values are within the limits defined in Table 2.9.47.-2.

CRITERIA

Apply the following criteria, unless otherwise specified.

The requirements for dosage form uniformity are met if:

1. the number of individual dosage units outside $(1 \pm L1 \times 0.01)T$ is less than or equal to $c1$; and
2. the number of individual dosage units outside $(1 \pm L2 \times 0.01)T$ is less than or equal to $c2$.

$c1$ and $c2$ for a given sample size *n* are defined in Table 2.9.47.-2. Unless otherwise specified, $L1$ is 15.0 and $L2$ is 25.0.

Table 2.9.47.-2 is to be interpreted as follows:

- for a sample size of $n = 400$, enter the table at $n \geq 394$: $c1 = 11$ and $c2 = 3$;
- for a sample size of $n = 450$, enter the table at $n \geq 434$: $c1 = 12$ and $c2 = 3$;
- for a sample size of $n = 500$, enter the table at $n \geq 490$: $c1 = 13$ and $c2 = 4$.

01/2020:20949

2.9.49. POWDER FLOW PROPERTIES BY SHEAR CELL METHODS

The methodology in this general chapter is based on standard test methods ASTM D6773-08 and ASTM D6128-14.

Powder flow properties play an important role in the design of formulations, processes and pharmaceutical production equipment, and an approach commonly used to characterise these properties is to submit the powder to shear tests, which are experiments designed to determine the flow properties of the powder by applying different states of stress and strain to it. Using these tests, a wide variety of parameters describing the flow properties of a powder can be studied, including the yield locus, the angle of internal friction, the compressive strength, the tensile strength, and a variety of derived parameters such as the flowability ratio. Because of the ability to control experimental parameters precisely, flow properties can also be determined as a function of consolidation load, time, and environmental conditions such as temperature and humidity.

Many suitable shear cell configurations and test methods are available; the most widely used are those based on the Jenike-type shear cell or on ring shear cells such as the Schulze-type ring shear tester.

PRINCIPLE

UNIAXIAL COMPRESSION TEST

The uniaxial compression test illustrates the concept of flowability. As shown in Figure 2.9.49.-1, a hollow cylinder (cross-sectional area A, internal wall assumed as frictionless) is filled with a powder. The powder is loaded by the consolidation stress (σ_1) in the vertical direction. The more the volume of the powder can be reduced, the more compressible the powder is. In addition to the increase in bulk density (ρ_b) from the consolidation stress, an increase in the strength of the powder is also observed. Hence, the powder is both consolidated and compressed through the effect of the consolidation stress.

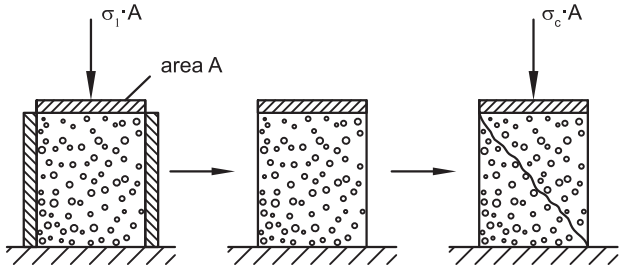

Figure 2.9.49.-1. – *Uniaxial compression test*

After consolidation, the powder is relieved of the consolidation stress (σ_1) and the hollow cylinder is removed. The consolidated cylindrical powder sample is subsequently loaded with an increasing vertical compressive stress and, at a certain stress, the sample fails along the shear plane and the powder starts to flow. The compressive strength (σ_c), or unconfined yield strength, is defined as the stress causing failure. Since the powder fails only at a sufficiently large vertical stress, there is a specific yield limit for the powder.

The yield limit of a powder is dependent on its stress history, i.e. its previous consolidation. The greater the consolidation stress (σ_1) the greater the bulk density (ρ_b) and compressive strength (σ_c). Thus, uniaxial compression tests conducted at different consolidation stresses (σ_1) yield different pairs of values (σ_1, σ_c) and (σ_1, ρ_b). Plotting these pairs of values as points in a (σ_1, σ_c) diagram and a (σ_1, ρ_b) diagram, respectively, and drawing in each diagram a curve through these points, usually results in curves similar to those shown for product A

in Figure 2.9.49.-2, where bulk density (ρ_b) and compressive strength (σ_c) typically increase with consolidation stress (σ_1). Very rarely a progressive slope similar to that of the left part of curve B is observed. The graph of σ_c versus σ_1 is called the flow function.

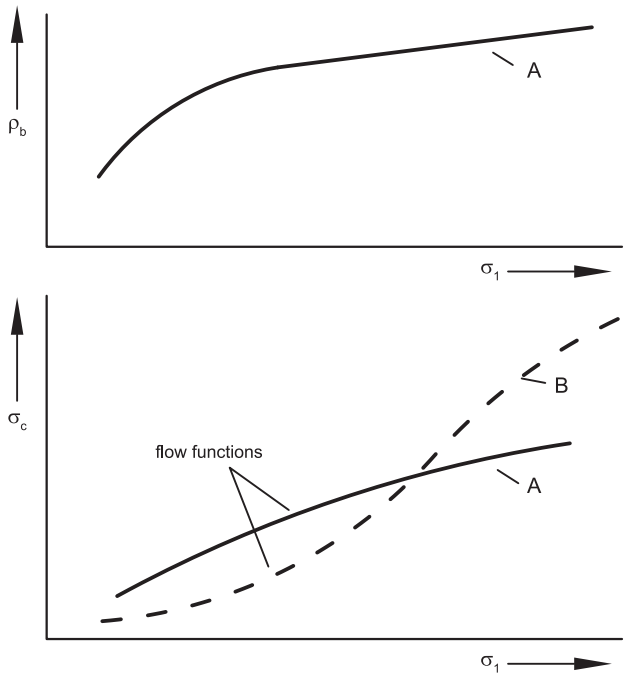

Figure 2.9.49.-2. – *Bulk density (ρ_b) and compressive strength (σ_c) as a function of consolidation stress (σ_1)*

NUMERICAL CHARACTERISATION OF FLOWABILITY

The flow function can be used to characterise the flow behaviour of a powder in terms of the flowability ratio (ff_c), which is given by:

$$ff_c = \sigma_1 / \sigma_c$$

The larger the ff_c, the better a powder flows. The ff_c value can be used to classify the flow behaviour as follows:

$ff_c < 1$	not flowing
$1 < ff_c < 2$	very cohesive
$2 < ff_c < 4$	cohesive
$4 < ff_c < 10$	easy-flowing
$10 < ff_c$	free-flowing

Figure 2.9.49.-3 shows the flow function A taken from the (σ_1, σ_c) diagram in Figure 2.9.49.-2. Additionally, the boundaries of the ranges of the classifications listed above are shown as straight lines, each representing a constant value of the flowability ratio (ff_c). This diagram clearly shows that the flowability ratio (ff_c) of a specific powder is dependent on the consolidation stress (σ_1) applied.

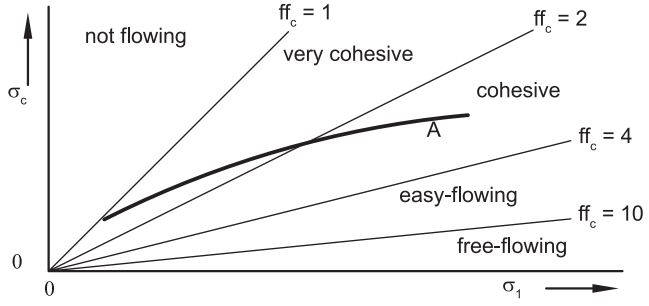

Figure 2.9.49.-3. – *Flow function and lines of constant flowability ratio*

Furthermore, the flow function may change depending on the consolidation time, for example, at the same σ_1 level, higher σ_c values may be obtained with longer consolidation times; this is known as the time consolidation effect. Possible mechanisms are solid or liquid bridges, solid crystallisation, viscoelastic or viscoplastic deformation, or chemical reactions at the particle contacts.

YIELD LIMIT AND MOHR STRESS CIRCLE

Assuming that the force of gravity and wall friction effects can be disregarded, the uniaxial compression test can be represented as shown in Figure 2.9.49.-4, in a (σ, τ) diagram where σ is the normal stress and τ is the shear stress. In such a diagram, all pairs of values (σ, τ) form a circle representing the stresses in the powder; this is called a 'Mohr stress circle'. The Mohr stress circle is centred on the sigma axis. The two intersect points with the sigma axis are called the minor and major principal stresses. Figure 2.9.49.-4 shows the Mohr stress circles corresponding to the uniaxial compression test and a possible yield limit of the sample (the real course of the yield limit cannot be determined with only the uniaxial compression test).

Mohr stress circle A describes the stresses in the powder sample at consolidation. Since no shear stress is applied, σ_1 corresponds to the normal stress or vertical stress (σ_v) and σ_2 corresponds to the horizontal stress (σ_h).

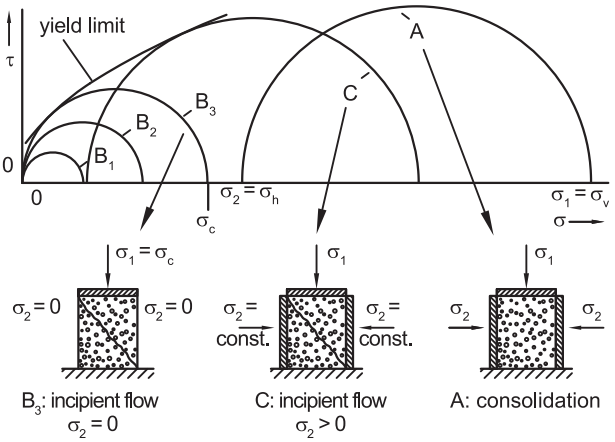

Figure 2.9.49.-4. – *Measurement of compressive strength and corresponding (σ, τ) diagram*

In the second part of the test shown in Figure 2.9.49.-1, the sample is loaded with increasing vertical stress after it has been relieved of the consolidation stress and the hollow cylinder has been removed. As the vertical load increases, the stress states at different load steps are represented by stress circles with increasing diameter (stress circles B_1, B_2, B_3 in Figure 2.9.49.-4). The minor principal stress, i.e. the horizontal stress, is equal to zero for all stress circles since the lateral surface of the sample is uncovered and not loaded.

Mohr stress circle B_3 represents the stresses in the powder sample at failure of the sample. Since the load corresponding to this Mohr stress circle causes incipient flow of the sample, Mohr stress circle B_3 must be tangential to the yield limit in the (σ, τ) diagram.

If, during the second part of the experiment shown in Figure 2.9.49.-1 (i.e. the measurement of compressive strength), a constant horizontal stress $\sigma_h > 0$ were also applied to the sample in addition to the vertical stress (σ_v), stress circles that indicate failure of the sample and are tangential to the yield limit (e.g. stress circle C in Figure 2.9.49.-4) would likewise be found. Thus the yield limit is the envelope of all stress circles that indicate failure of a powder sample.

MEASUREMENT WITH A SHEAR TESTER

PRINCIPLE

The test sample must be representative of the powder with respect to particle-size distribution, moisture, temperature and other properties that may have an influence on the flow behaviour. The test sample is filled into a shear cell of circular or annular cross-section, depending on the type of tester used. In order to achieve a homogenous and representative powder bed, filling should be carried out uniformly in small horizontal layers using a spoon or spatula, without applying force to the surface of the material, until the cell is slightly overfilled. Excess powder is then removed by scraping off with a blade until the powder is flush with the top of the shear cell. The shear cell is then completed with a lid placed on top of the sample. The latter step may vary with the type of apparatus and is therefore carried out according to the manufacturer's instructions to achieve a homogenous and representative powder bed.

In general, a shear test measures the yield limit of a consolidated powder bed. This yield limit is also called the yield locus. It depends to a certain extent on the apparatus and experimental conditions. Typically the yield locus is measured immediately after consolidation of the powder bed. If however the yield locus is measured after a certain consolidation time, then it is called the time yield locus. When running a shear test, a normal stress (σ) is applied vertically to the powder in the shear cell. A shear deformation of the sample is then induced by moving the lid of the shear cell relative to the bottom of the shear cell in a horizontal direction with constant velocity (*V*) (see Figure 2.9.49.-5). This results in a horizontal shear stress (τ), which develops due to the friction between the particles in the shearing plane. The lid of the shear cell is allowed to move vertically in order to adjust to changes in the sample's bulk density.

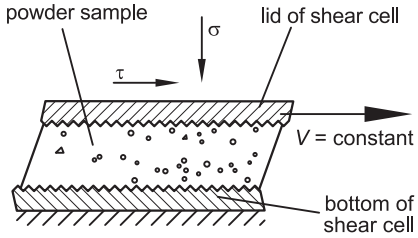

Figure 2.9.49.-5. – *Principle of shear deformation in a shear cell*

When a point of a yield locus is measured, as in the uniaxial compression test, 2 steps are necessary: first the powder sample is consolidated in a preshear step, and then a point of the yield locus is measured in a shear or shear-to-failure step.

PRESHEAR STEP

For preshear, the powder sample is loaded in the vertical direction under a well-defined normal stress ($\sigma = \sigma_{pre}$), and is then sheared. Preshear is stopped when steady-state flow, characterised by constant shear stress (τ_{pre}), is achieved. The pair of values of normal stress and shear stress at steady-state flow (σ_{pre}, τ_{pre}) is plotted in a normal stress - shear stress diagram ((σ, τ) diagram, Figure 2.9.49.-6, right). Point (σ_{pre}, τ_{pre}) is called the preshear point.

SHEAR-TO-FAILURE STEP

After the powder has been consolidated by the preshear procedure, the shear stress (τ) is reduced to zero by reversing the relative motion of the lid with respect to the bottom of the shear cell.

For the next step of the test procedure, the so-called shear or shear-to-failure step, the normal stress acting on the sample is decreased to a value σ_{sh}, which is less than the normal stress at preshear (σ_{pre}).

If the consolidated sample is sheared under the normal stress $\sigma_{sh} < \sigma_{pre}$, it will start to flow when a sufficiently large shear stress (τ_{sh}) is attained. At that point particles start to move against each other. The material will start to dilate, i.e. decrease in bulk density and shear resistance, and thus shear stress will decrease. The maximum shear stress (τ_{sh}) characterises incipient flow. The corresponding pair of values (σ_{sh}, τ_{sh}) is a point of the yield locus in the (σ, τ) diagram (Figure 2.9.49.-6, right). Such a point is called a shear point or a point of incipient flow.

In order to measure the course of the yield locus, several of the tests described above must be performed, where the samples must first be consolidated at the same normal stress (σ_{pre}, preshear). Then the samples are sheared to failure under different normal stresses $\sigma_{sh} < \sigma_{pre}$. The yield locus follows a curve plotted through all measured shear points (Figure 2.9.49.-6, right). In general, at least 3 shear points should be measured.

With the Jenike-type shear cell a new sample has to be prepared for each shear point (indicated as 'next test' in Figure 2.9.49.-6). However, with ring shear testers a complete yield locus is usually measured with 1 sample. In addition, with the Schulze-type ring shear tester the bulk density is measured during the test, depending on the consolidation stress applied.

DATA EVALUATION

Parameters that describe the flow properties can be determined from the yield locus as shown in Figure 2.9.49.-7.

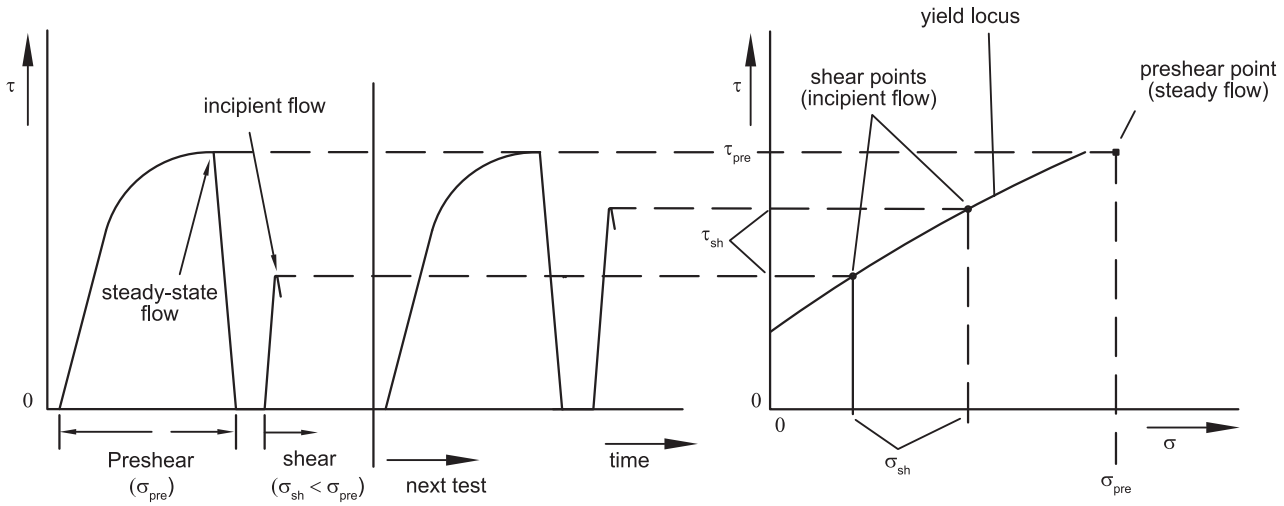

Figure 2.9.49.-6. – *Plot of shear stress versus time (left) and corresponding yield locus (right)*

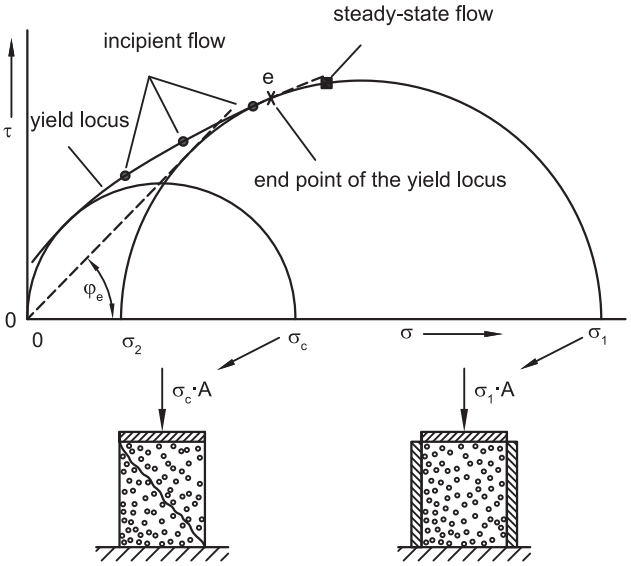

Figure 2.9.49.-7. – *Yield locus, Mohr stress circles and analogy with uniaxial compression test*

The consolidation stress (σ_1) is equal to the major principal stress of the Mohr stress circle, which is tangential to the yield locus, and intersects at the point of steady-state flow (σ_{pre}, τ_{pre}). This stress circle represents the stress distribution in the sample at the end of the consolidation procedure (stresses at steady-state flow). It corresponds to the stress circle at the end of consolidation in the uniaxial compression test.

The compressive strength (σ_c) is determined from the stress circle that is tangential to the yield locus and runs through the origin (minor principal stress $\sigma_2 = 0$). This stress circle represents a similar stress state to the one that prevails in the second step of the uniaxial compression test.

A straight line through the origin of the (σ, τ) diagram, tangent to the greater Mohr circle, is the effective yield locus, shown as a broken line in Figure 2.9.49.-7. It encloses the σ-axis with the effective angle of internal friction (φ_e). Because the largest Mohr stress circle indicates a state of steady-state flow, the angle φ_e can be regarded as a measure of the internal friction at steady-state flow.

Further flow properties can be determined from the yield locus as illustrated in Figure 2.9.49.-8.

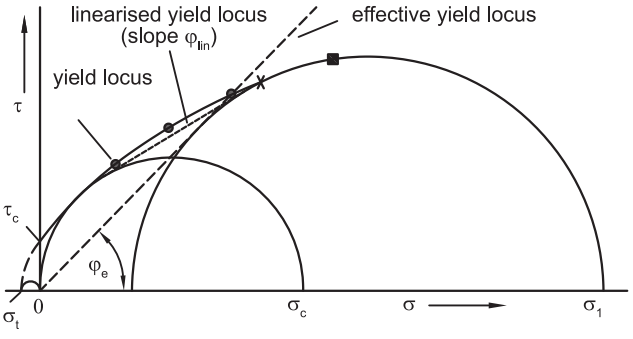

Figure 2.9.49.-8. – *Yield locus and characteristic values for flow properties*

For many applications the yield locus is linearised as the tangent to both Mohr circles. The linearised yield locus is characterised by its slope angle φ_{lin}.

The cohesion (τ_c) is the value of the shear stress where the yield locus intersects with the τ-axis, i.e. at normal stress $\sigma = 0$. The uniaxial tensile strength (σ_t) is the normal stress at the left end of the yield locus at shear stress $\tau = 0$. As it is difficult to measure the yield locus at small and negative stress levels, cohesion may be obtained by extrapolating the yield locus to the intersection with the τ-axis. Due to the pronounced non-linearity of the yield locus at low stresses, the cohesion obtained in this way is less accurate than the compressive strength, and it is hardly possible to determine tensile strength by extrapolation.

If several yield loci are measured at different stress levels, i.e. with different normal stresses at preshear (σ_{pre}), each yield locus represents another state of consolidation and another bulk density. The above-mentioned flow properties, namely compressive strength, effective angle of internal friction or slope angle of the linearised yield locus, can be indicated as functions of the consolidation stress (σ_1), similar to Figure 2.9.49.-2 where bulk density and compressive strength are plotted versus consolidation stress.

01/2020:20952

2.9.52. SCANNING ELECTRON MICROSCOPY

This general chapter focuses on scanning electron microscopy applied to pharmaceutical materials, from research to quality control.

Scanning electron microscopy (SEM) is a powerful imaging technique that is superior to and complements light microscopy in terms of resolution, magnification and depth of field.

In addition, by exploiting the different interactions between the electrons and the specimen, it provides topographical and compositional information and can thus also be used as an analytical tool. When it is combined with elemental X-ray microanalysis, in particular, chemical analysis can be performed (see general chapter *2.2.37. X-ray fluorescence spectrometry*).

SEM is a well-established technique and, increasingly, it is being applied to examine and characterise a wide range of pharmaceutical materials in solid form but also, with the use of specialised specimen preparation methods, in semi-solid and liquid form.

PRINCIPLE

To produce magnified images, a scanning electron microscope uses a finely-focused beam of accelerated electrons instead of light; the specimen is scanned (rastered) in a rectangular pattern with the electron beam. This technique exploits the interactions between the electron beam and the specimen using different types of detectors. Due to the nature of these interactions, a variety of signals are produced and these can be used to provide characteristic information about the specimen at and from just below its surface.

INTERACTION WITH THE SPECIMEN

As the surface of the specimen is scanned by the electron beam, these electrons (also known as primary electrons) interact with the specimen and can penetrate to a depth of up to a few tens of micrometres. Electrons are scattered and absorbed within a teardrop-shaped volume just below the surface of the specimen, known as the interaction volume (Figure 2.9.52-1). The depth to which the electron beam penetrates is directly proportional to the beam voltage (a high-energy beam will penetrate deeper than a low-energy beam) and inversely proportional to the average atomic number of the constituent elements of the specimen (the beam will penetrate much deeper into a specimen rich in light elements than into one rich in heavy elements).