

Transmission Electron Microscopy



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Analytical Technologies Limited

An ISO 9001 Certified Company

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►► **TEM revolutionizes access to transmission electron microscopy**

- Transmission Electron Microscopy (TEM) is unmatched in providing high resolution images that allow visual insights into sample morphology of nano-sized particles. However, due to the need for considerable operator skills, special laboratory facilities, and the limitations in providing quantitative data it is not routinely used in process development. TEM analysis is typically performed in specialized TEM facilities and time to result is often long.

TEM offers an in-house solution that enables non-experts in electron microscopy to rapidly obtain meaningful nanoparticle characterization data. It automatically images, detects and analyzes particles with defined morphological characteristics and transforms the data into accurate metrics. TEM is designed to be placed close to your process in a standard laboratory setting.

- **TEM in process development :** TEM complements existing routine analysis methods in process development. The system can be set up to automatically give you detailed information about the morphology, integrity and purity of your nanoparticles. In a few hours you generate quantitative data and images of your particles that can support decision making in the optimization of your process.
- **TEM as a screening tool:** TEM can rapidly screen and acquire thousands of images to give an accurate representation of your samples. The acquired images are analyzed instantly to give meaningful results.
- **TEM in quality control:** Automated analysis of a large number of images and particles is set to reach statistical convergence and produce objective results without the risk of human error. This makes MiniTEM suitable in control of critical quality attributes.



- **Save time :**
 - Instant results – adjust your process within a few hours
 - No waiting for service supplier
 - Automation frees up your time to other tasks
- **Increase reliability :**
 - See your product and your process
 - Objective quantitative data
 - Confirm critical quality attributes
- **Make it easier :**
 - Less focus on the technology and more on the results
 - Automation allows non-expert operation
 - Minimized risk for human error

►► **Broad applicability across many industry segments**

- With TEM you can analyze both biological and non-biological samples. The system offers simplicity and versatility while providing the analyst key insights into important aspects of particle characterization at any step of the process. These insights include:
 - Overall morphology and particle integrity
 - Particle size distribution
 - Sample purity
 - Virus quantification
 - Reveal undesired process outcome such as particle clustering or aggregation

Biopharmaceutical industry

- **Gene therapy** – control the effects of bioprocess conditions on your viral vectors
- **Vaccines** – monitor changes in morphology of live viruses and their interactions with adjuvants throughout production
- **Recombinant proteins** – analyze particle aggregation of small proteins
- **Cell sections** – improve contamination control for upstream process development
- **Drug delivery nanoparticles** – perform accurate particle size and shape distribution analysis

Material industry

- Characterize both biological and nonbiological particles e.g. nanopolymers, gold nanoparticles, nano-coating and graphene

Pathology

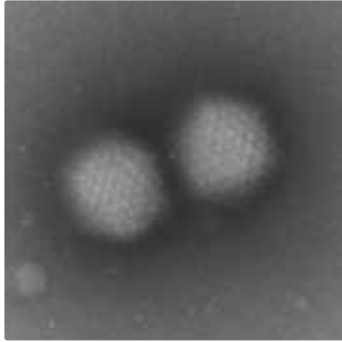
- TEM supports both analysis of biological fluids and tissue sections in diagnostic medicine

CRO services

- Retrovirus detection of master cell banks and unprocessed bulk harvest samples

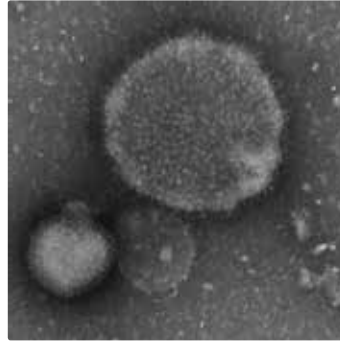
►► TEM example images

Non-enveloped viruses



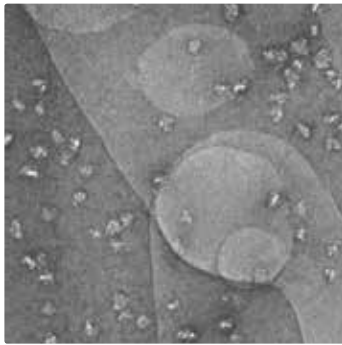
Adenoviruses (~90 nm)

Enveloped viruses



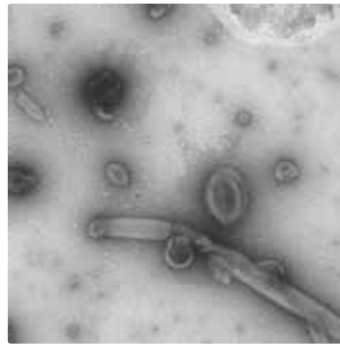
Influenza virus (~110 nm)

Recombinant proteins



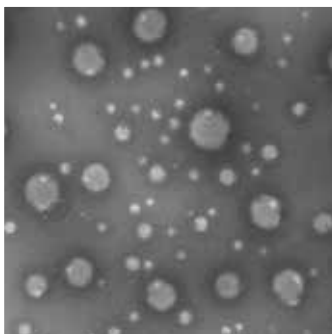
Small proteins (~250kDa)

Lipid vesicles



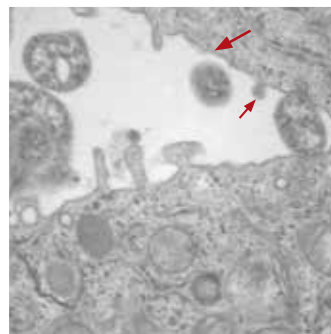
Tubular and round lipid nanovesicles

Drug delivery nanoparticles



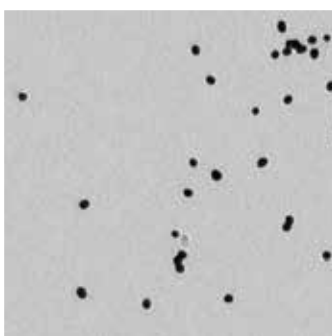
Lipid nanoparticles

Tissue sections



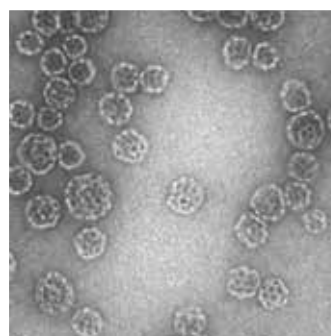
Retrovirus contaminated production cell line

Inorganic nanoparticles



20 nm gold particles

Vaccine adjuvants



Immuno-stimulatory complexes

►► Simple work flow from sample preparation to particle analysis

When performing TEM analysis, users can either use unstained samples or follow a quick and simple standard sample preparation method called negative staining. The purpose of the staining is to give support and give contrast. In this procedure the sample is applied to a standard 3.05 mm Ø grid support and treated with the staining agent.

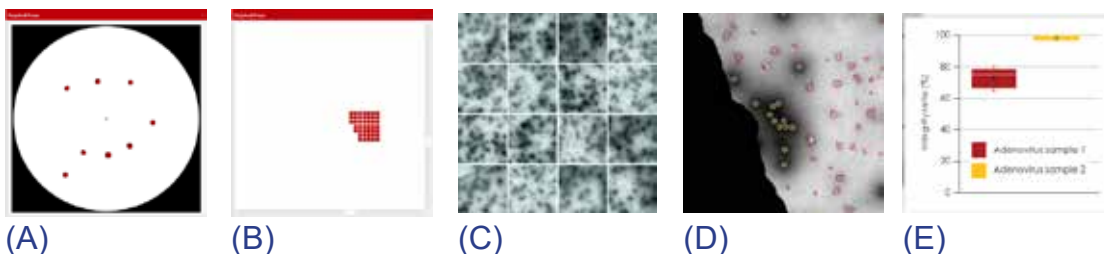
- Analyze samples un-stained or stained with contrast agent
- Sample preparation in 5 minutes
- Load the grid in the sample holder and insert it into TEM
- Explore samples both in solution and in tissue
- Reveal undesired process outcome such as particle clustering or aggregation

When the sample has been transferred into the TEM system the operator can perform particle analysis either manually or using the powerful automated particle analysis features that TEM offers.

The user can conveniently pre-select imaging waypoints and set the number of images to be automatically acquired at each waypoint. TEM moves to each waypoint and collects the set number of images. Importantly, the automated imaging can subsequently be coupled to suitable particle detection methods designed for particle screening and measurements.

A large number of particles and structures of interest present in the samples is easily detected and quantified.

When enough data has been gathered to provide meaningful statistical representation, the images, together with the particle measurements for the sample, can be plotted and presented graphically to support decision making.



(A) Way points are selected. (B) Images are automatically acquired in selected way points. (C) A large number of images are obtained. (D) Particles are detected and classified in the images. (E) Defined morphological characteristics are transformed into accurate metrics.

►► TEM operation overview

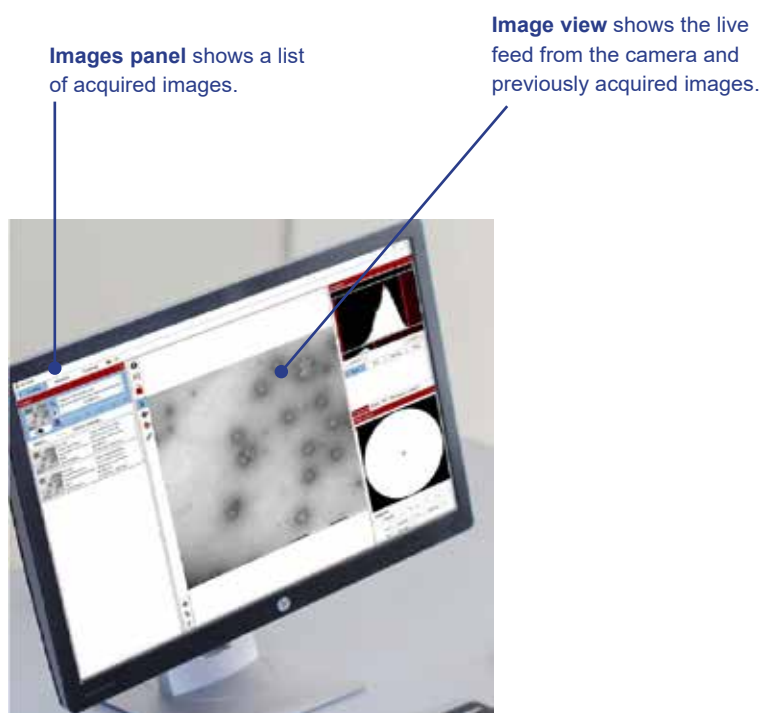
TEM allows you to work with the system in three different modes:

Imaging – In this mode you can view and explore the sample.

Analysis – In this mode you can analyze acquired images and choose different graphical presentations of your data.

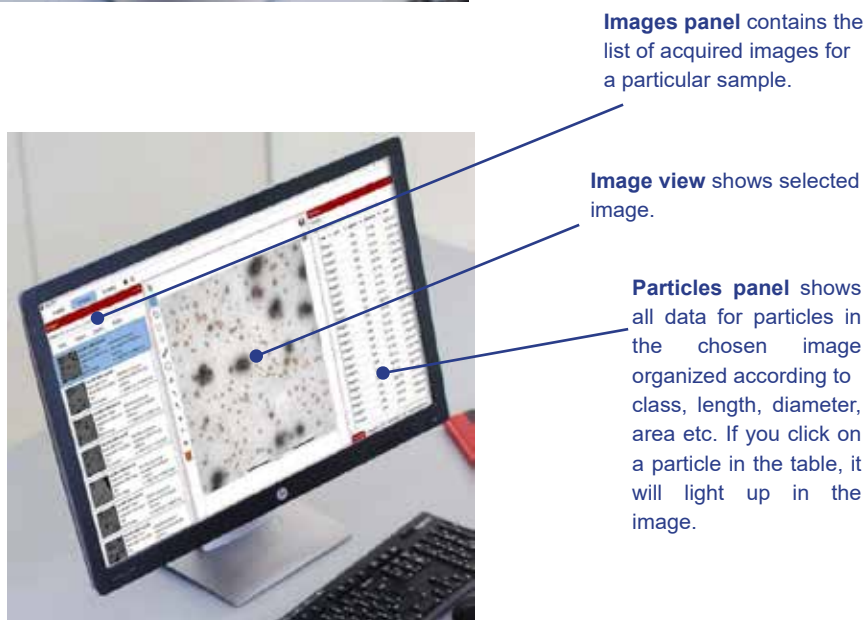
Scripting – In this mode you can choose to run a method script from the library or build your own tailored script.

Imaging mode: In the imaging mode you can see the live view of your sample and inspect all acquired images.



Analysis mode

In the analysis mode you can review acquired images and particle data. All data can also easily be exported to commonly used file formats.





Plot panel

There are a number of options for graphical presentation of the data.

- Histogram plot
- Bar plot
- Box plot
- Scatter plot

Scripting mode

When you perform a TEM analysis you can use an existing script or you can design your own tailored script. A library of modules for different operations are easily connected by dragging and dropping them into a preferred configuration.



Modules panel contains list of available script building modules. The output of the individual modules is defined and clearly described to support easy configuration of a customized script

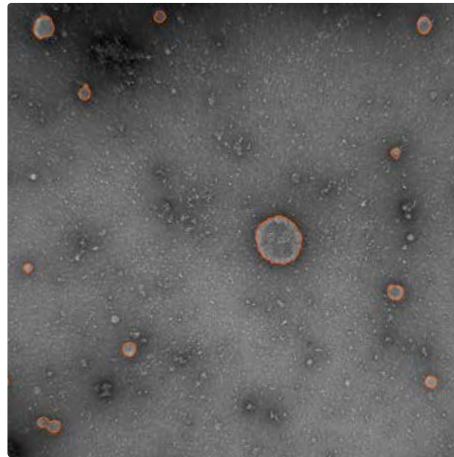
Scripting view shows the design area where modules are combined and configured into a complete script.

Preview Panel shows the result of each module output at design and during the run of the script.

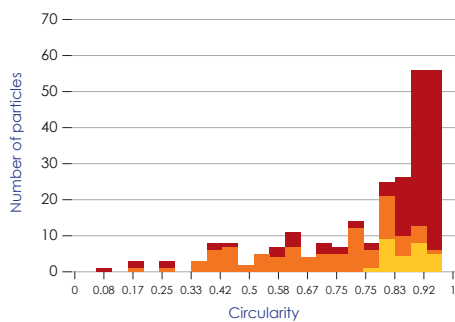
►► TEM applications for viral vaccine and gene therapy development



Particle integrity based on shape



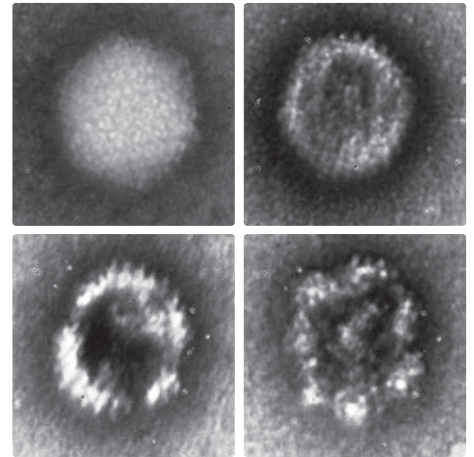
Influenza vaccine candidate



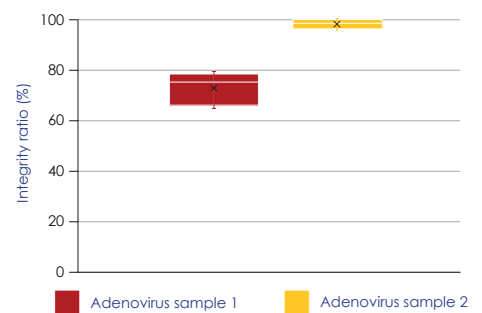
Enveloped viruses used for vaccine development are more sensitive to environmental conditions and may lose infectivity through impairment of their envelope during the manufacturing process.

Morphology variations (e.g. size and shape) of influenza viruses are automatically analyzed and quantified with the TEM system.

Particle integrity based on staining pattern



Adenoviruses

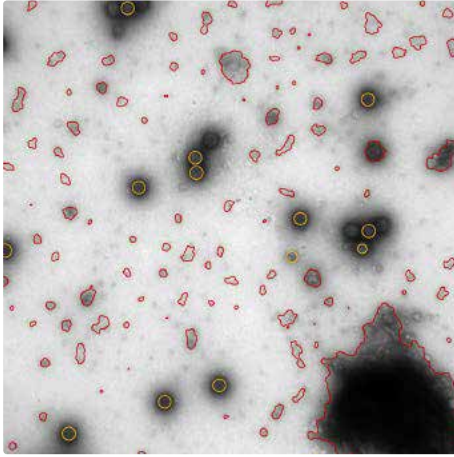


Proportion of intact Adenovirus particles in two different samples.

Non-enveloped viruses used as gene therapy vectors e.g. adenoviruses can easily lose their structural integrity. Particle integrity of viruses is critical for the delivery of genetic material and thus determines their therapeutic performance.

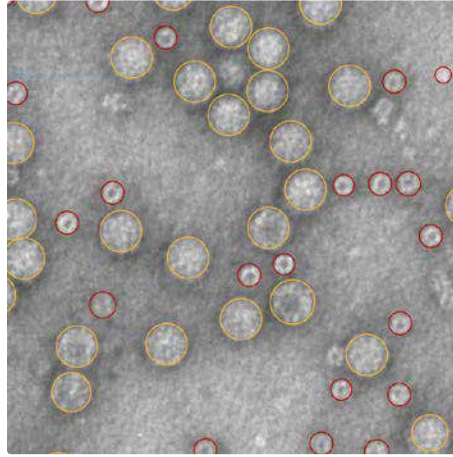
With TEM, overall particle integrity of viral vector products is monitored.

Purity and aggregation



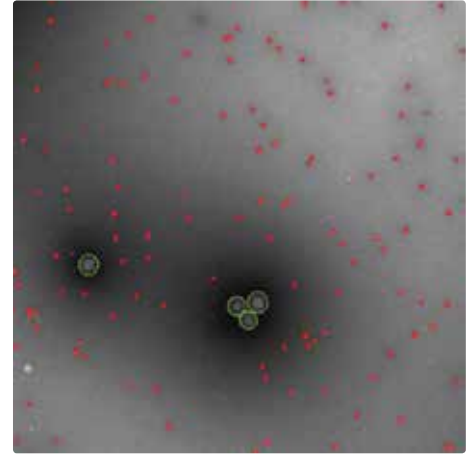
Adenoviruses before purification step

Hidden contaminants

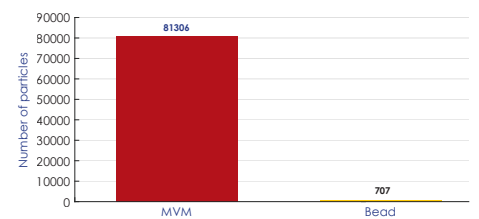
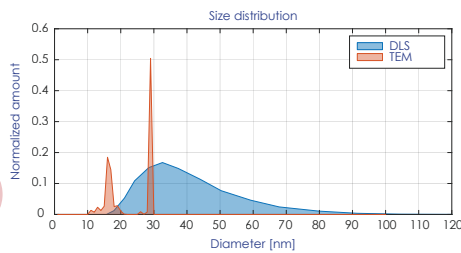
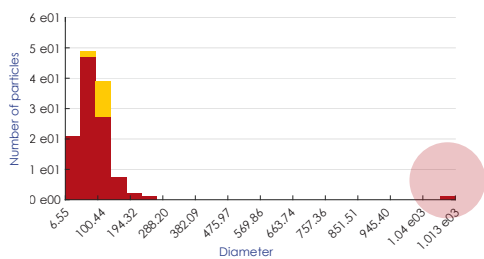


Host cell contaminants and AAV's

Virus quantification



Viruses and reference nanoparticles



Particles present in the sample that deviate from the expected size and shape can be the undesired outcome of an un-optimized process step. In this example of an adenovirus sample, a large aggregate as well as smaller size debris are detected and automatically measured.

Automated analysis using TEM can reveal hidden contaminants. In this case a sample of adeno-associated virus particles is shown to contain smaller sized proteasomes. The graph shows comparing data of TEM and DLS analysis where the two particle populations are differentiated by TEM where DLS analysis only shows one broad peak.

Counting whole virus particles with TEM for virus quantification purposes typically involves spiking virus samples with a reference nanoparticle standard with a known concentration to which the virus count is correlated. Performing this manually is time consuming. TEM offers fast and automated virus quantification.

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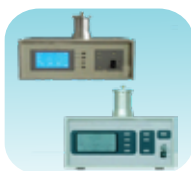
Atomic Absorption
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Liquid Particle
Counter



Optical Emission
Spectrophotometer



DSC/TGA



Semi Auto Bio
Chemistry Analyzer



HEMA 2062
Hematology
Analyzer



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URINOVA 2800
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Total Organic
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Water purification
system

Regulatory compliances



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