DEKATI
Excellence in Particle Measurements

Dekati Ltd Application Note

ELPI IN PHARMACEUTICAL MEASUREMENTS

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Introduction

ELPI™ (Electrical Low Pressure Impactor) is an instrument to measure particle size distribution and concentration in real-time. The operating principle of the ELPI is based on particle charging, size classification in an inertial low-pressure impactor, and current measurement with a sensitive multi-channel electrometer (*Keskinen et. al. 2001, Baron et. al. 2001*).

One of ELPIs main applications is pharmaceutical inhaler studies. In this application the ELPI™ can be used to detect particle number concentration and size distribution of inhaler particles in real-time and thus study e.g. the repeatability of an inhaler device. The instrument detects particle concentration and size distribution once per second. In addition, the ELPI™ has a unique capability of being able to measure the charge distribution of particles in real-time.

ELPI™ Specifications

- Particle size range 30nm –10 µm, with filter stage 7nm - 10µm.
- Number of stages: 13, 12 with electrical detection
- Sample flow rate: 10 or 30 lpm
- Collection plate diameter: 25mm

Figure 1. ELPI™ (Electrical Low Pressure Impactor).

ELPI™ Impactor

In pharmaceutical inhaler studies many different types of gravimetric impactors are commonly used to measure the particle size distribution. The ELPI™ impactor operates in exactly the same way as other impactors but it has as improved mechanical design compared to older commercially available impactors. The ELPI™ impactor has 13 stages, 12 of which have electrical detection to produce real-time data. The size range of the ELPI™ instrument, and therefore the impactor, is 30nm – 10µm. With an additional accessory, the filter stage, the size range can be extended down to 7nm (see details on the next page). When filter stage is used, stage number 12 is removed making the uppermost stage size bin wider, 4-10µm. Table 1 presents the differences between the ELPI™ impactor and Andersen Mark II impactor, commonly used in pharmaceutical measurements. Note that the stage numbers are reversely numbered.

ELPI™ Stage numbers	D50%
	µm
1	0.03
2	0.063
3	0.109
4	0.173
5	0.267
6	0.407
7	0.655
8	1.021
9	1.655
10	2.52
11	4.085
12	6.56

Andersen Mark II Stage numbers	D50%
	µm
7	0.4
6	0.68
5	1.11
4	2.07
3	3.27
2	4.69
1	5.87
0	9.03

Table 1. Stage numbers and D50% cutpoints of the ELPI™ impactor and Andersen Mark II impactor.

ELPI™ impactor calibration and quality control

The collection efficiency curves for ELPI™ impactor have been defined by an electrical method (Marjamäki et. al 2000). The resulting calibration curves can be found in Figure 2. The shape of the calibration curves can always be assumed to remain the same as long as the impactor design stays the same. The design of all ELPI™ impactors dedigned for the same flow rate is the same, and therefore the determination of calibration curves for each individual impactor is not required. However, due to small discrepancies that may happen during manufacturing process, a pressure calibration of each individual impactor is performed before the delivery of each impactor unit.

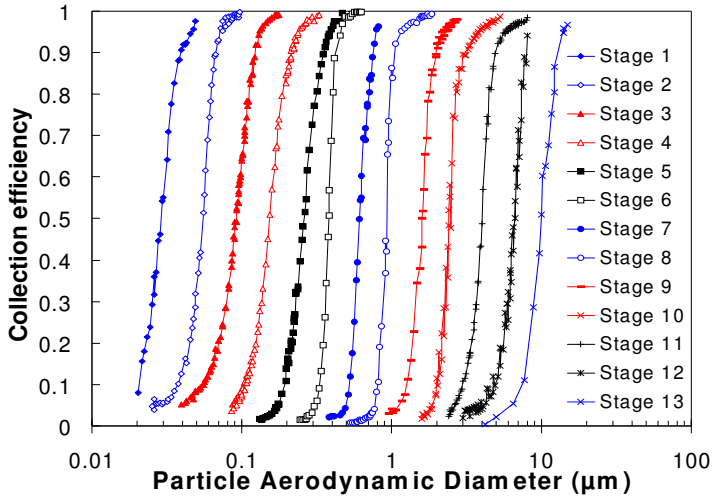
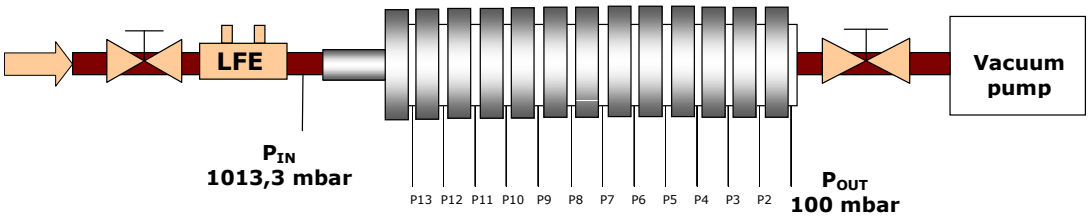


Figure 2. ELPI™ Impactor calibration curves. Data courtesy of Marjamäki et al.

The pressure calibration

The ELPI™ impactor is a low pressure impactor. The sample flow rate of the impactor is controlled by adjusting 100mbar below lowest impactor stage (stage 1). In these conditions, the stage number 1 acts as a critical orifice and the flow rate stays constant as long as the impactor does not leak, and it is kept clean so the impactor jets are not clogged. Therefore no other flow control device is required when the impactor is used. In the pressure calibration performer for each impactor unit, the exact impactor flow rate is measured with a laminar flow element while the pressure readings between each impactor stage are measured. The information retrieved from these measurements enables the calculation of the exact D50 values for each impactor unit (see Figure 3).



$$D_{50}\sqrt{C_c} = \sqrt{\frac{9\eta D_j (Stk_{50})}{\rho_p U}}$$

Where:

U =	Velocity of gas (result from pressure calibration)
D50 =	D50 cutpoint of the impactor stage
ρp =	Particle density
Dj =	Size of the body (nozzle)
η =	Gas viscosity
Cc =	Slip correction factor

Figure 3. Impactor pressure calibration setup.

ELPI™ quality control

The quality of the data measured with the ELPI™ can be verified by following the ELPI™ service program specified in the ELPI™ user manual. ELPI™ service program consist of two main parts: service done by the end-user, and the full calibration at Dekati Ltd or its qualified distributor.

The service done by the user of the instrument includes e.g. cleaning of the instrument, leakage check of the instrument and zero concentration check before the measurement. Following these procedures, the user can easily verify that the instrument is operating properly. Deviations from normal operating conditions can be detected if the pre-measurement checks are performed according to the instructions given in the ELPI™ user manual.

The ELPI™ full standard service that is performed at Dekati, or by its qualified distributor, includes e.g. calibration of all electronics, re-calibration of the impactor and reference check against a reference ELPI™ instrument to finally verify the result. The full standard service should be performed every 2-3 years to ensure correct operation of the instrument.

ELPI™ configuration

ELPI™ instruments are available with two different sample flow rates; either 10 lpm or 30 lpm. The 10 lpm ELPI™ was originally designed for high concentration measurements whereas the 30 lpm is mostly used in low concentration measurements. For pharmaceutical measurements, however, the 30 lpm version is recommended. The standard sample flow rate in many pharmaceutical measurements is close to 30 or 60lpm, and therefore using a 30lpm ELPI™ is more convenient than a 10lpm flow rate ELPI™. However, the 10lpm can also be used in inhalation aerosol measurements since the operating principle of these two instrument versions is exactly the same.

Optional accessories for pharmaceutical studies

Filter stage

The standard ELPI™ measurement range is 30 nm –10 µm. With the filter stage accessory this measurement range can be extended down to 7 nm, but the installation of the filter stage requires removal of stage number 12, and therefore size resolution is diminished in the large particle sizes. The filter stage is recommended if formulations that produce very small particles are measured, for measurement of larger particle sizes the filter stage is not required. If the filter stage is installed in the impactor, however, the user can still very easily modify it back to the standard configuration by only changing few parts in the impactor. (Marjamäki et. al. 2002)

Figure 4. ELPI filter stage parts.

USP inlet

A USP inlet to be used together with the ELPI™ is available at Dekati Ltd.

Polycarbonate and aluminium foils

Although the use of the ELPI for real-time concentration measurements does not require use of collection foils on the impactor stage, the collection foils are recommended to be used on the impactor collection plates to make the impactor cleaning intervals longer and optimize the operation. Especially in pharmaceutical measurements where the measured particles can be hard and solid, greasing of the collection foils is recommended to prevent particle bounce. In ELPI™ measurements where only electrical or gravimetric data is needed, greased aluminium foils should be used - if chemical analyses that can't be performed from aluminium foils are made, e.g. polycarbonate collection foils can be used instead. Dekati Ltd has aluminium and polycarbonate foils available for the ELPI™ collection plates, as well as Apiezon-L grease for greasing the foils.

Figure 5. ELPI impactor collection plate with an aluminium collection foil.

ELPI™ data

The ELPI™ instrument can be used to provide three different types of data; electrical real-time concentration data, particle charge distribution data or gravimetric mass size distribution data. The ELPI™ electrical data is always obtained when the charger is kept on. The particle charge distribution data is obtained if the charger is switched off. The gravimetric data can be obtained if the collection foils are weighed before and after the measurement.

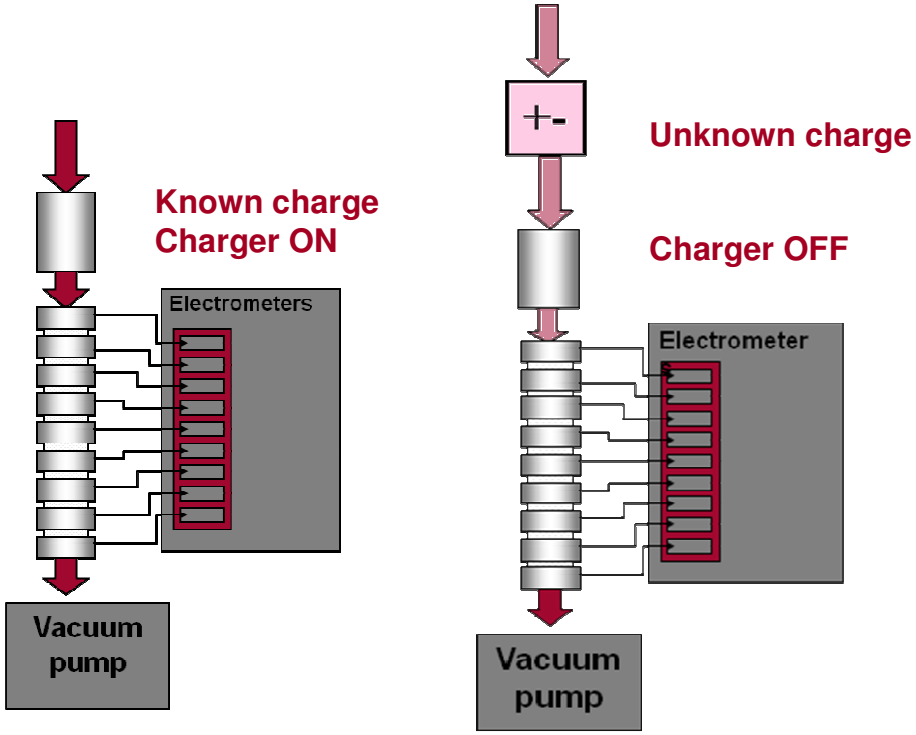


Figure 6. Two different ELPI™ setups. On the left the ELPI™ is used with charger ON and particle real-time number concentration is measured. On the right the charger is switched off, and the particle inherent charge distribution is measured. With charger off, the particle gravimetric size distribution can also be measured.

ELPI™ real-time data – Number concentration

The most common way to operate the ELPI™ is to charge the particles (charger on) and then size classify them in the impactor. This way the user will get information once per second on the particle number size distribution in 12 different size fractions. Figure 7 shows one example of this type of data. Particle mass size concentration and size distribution can also be calculated from the calibrated number concentration data making certain assumptions on particle size and shape.

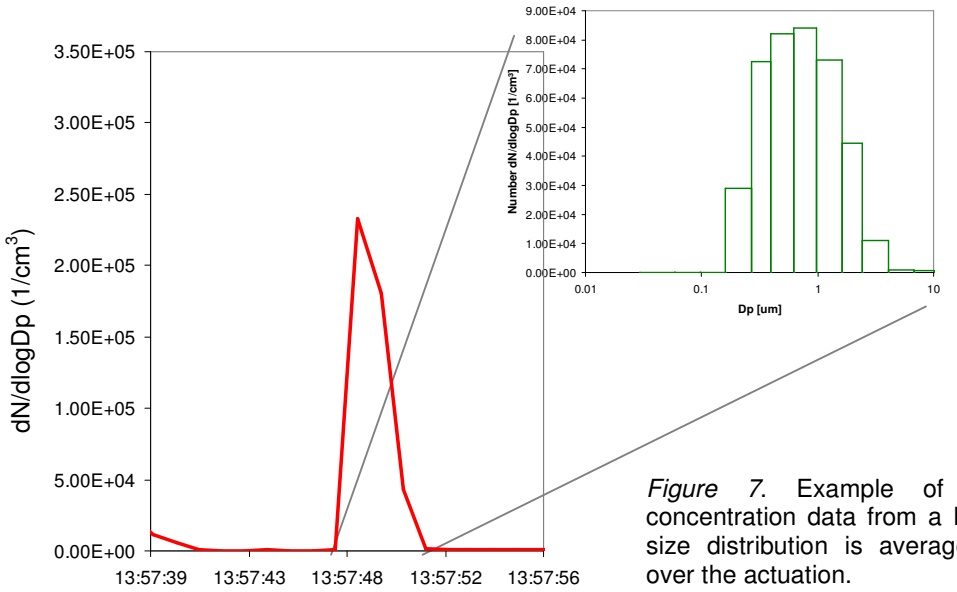


Figure 7. Example of particle number concentration data from a DPI actuation. The size distribution is average size distribution over the actuation.

The ELPI™ real-time operation mode can be used e.g. to study the repeatability of multiple actuations.

Particle charge size distributions

ELPI™ instrument can be used to measure particle charge levels in real-time by switching the charger off. In this setup no real-time number concentration data is obtained but particle charge levels, both negative and positive levels, can be measured in different impactor stages (particle size fractions) since the electrometers still operate measuring the current signal from all the stages. The result in one impactor stage is the net charge of particles in that particular size class. The electrometers can measure very small current signals (±1-2fA) so very small charge levels on particles can be detected. (*Mikkanen et. al. 2003 and 2004*)

Example data on pharmaceutical inhalation aerosol charge measurements using ELPI™ is presented in Figures 8 and 9.

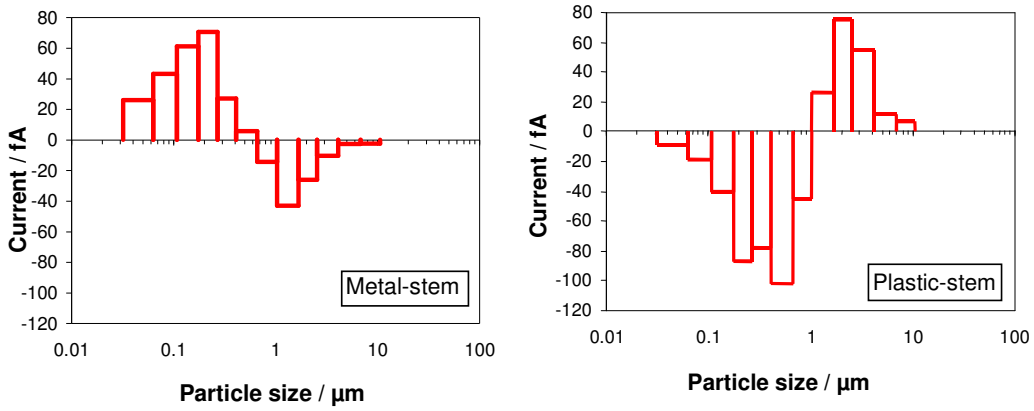


Figure 8. Particle charge distributions of two MDIs with same formulation and almost the same inhaler devices - only different stem material is used in the device. Metal-stem was used in the data measured in the left, and plastic stem in data measured in the right. Data courtesy of AstraZeneca – M.Svensson&L.Asking.

In pharmaceutical inhaler studies measuring the particle charge distribution can be of great importance. It has been suggested that the charge level carried by particles, among other particle characteristics, may have effect on inhalation efficiency of the particles, and therefore the delivery of the drug into the respiratory tract. Depending on the type of inhaler, the particle charging process can be complex and happen with various different mechanisms depending e.g. on the materials both in the inhaler device and the used drug/formulation. Charging can happen for example by contact of materials; insulating liquids and powders can be collected on charged surfaces and be further re-entrained carrying an unknown amount of charge. The charge density in the particles can also be increased if particle contains volatile material that is evaporated from the particles. All in all, the charging mechanisms are complex and very difficult to estimate, but actual measurements are necessary if information on the charge level of the particles is wanted. (*Glover et. al. 2004*)

An example of a real-time charge distribution measurement using the ELPI is presented in Figure 9. The y-axis is in femto-amperes (fA), and the data is measured once per second.

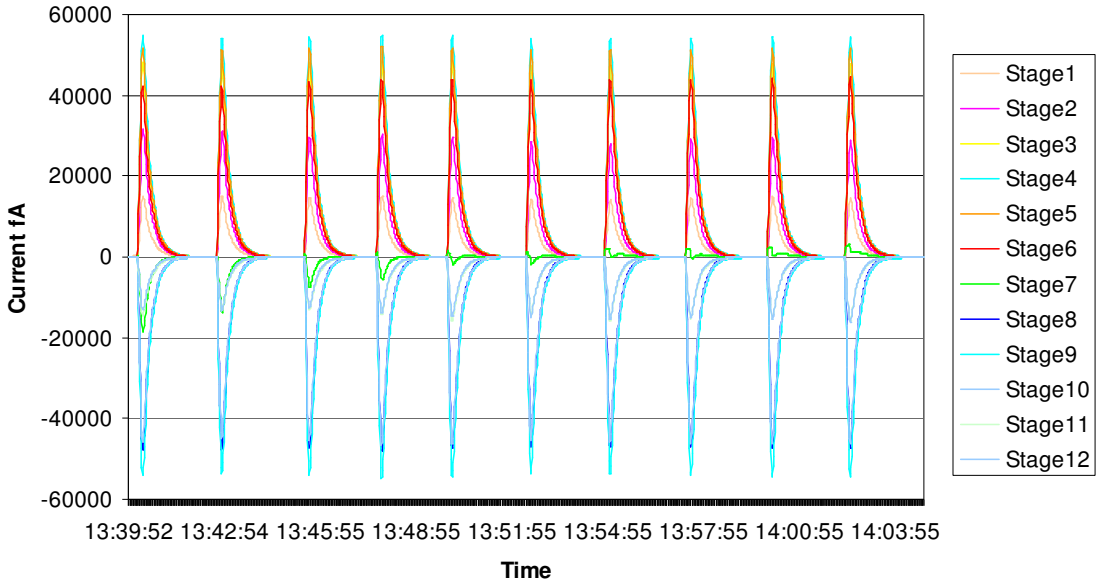


Figure 9. Measurement of the repeatability of charge distribution produced by an MDI. Data courtesy of Glaxo Smith Kline.

Particle mass size distributions

Information on particle mass size distribution can be gained in two ways using the ELPI™; using the electrical real-time data, or making a gravimetric measurement with the ELPI™ impactor.

1. Gravimetric measurement with ELPI™

ELPI™ impactor can be used as a gravimetric impactor to obtain gravimetric mass size distribution of the sample by weighing the impactor collection foils before and after the measurement. In this setup, the charger must be switched off to avoid any particle losses in the charger, which in standard ELPI™ real-time measurement are compensated for in the software. Since the charger is switched off, no real-time number concentration data is obtained, but instead the charge distribution of the particles is measured. If gravimetric measurements are made with the charger on (measuring the real-time number concentration of particles at the same time) the gravimetric results need to be corrected for the size dependent particle losses in the charger. The charger penetration curve is available for all users at Dekati Ltd.

In gravimetric measurements collection foils (ø25mm) need to be used on the collection plates. Aluminium and polycarbonate foils are commonly used but other types of foil/filter materials can be used as well. The only restrictions are that foils should be thin enough (max 0.1mm) and their surface smooth to avoid any possible changes in impactor calibration values. More information on suitable filters and foils for the ELPI impactor can be found in the technical note: Substrates and filters for Dekati Impactors.

ELPI™ impactor is also available without the ELPI™ electronics cabinet for gravimetric use only. The impactor is called Dekati® Low Pressure Impactor (DLPI) and it has 13 stages in the size range of 30nm-10µm. The DLPI impactor can be upgraded into a

complete ELPI™ unit and the price of the impactor will then be fully compensated upon the purchase of the ELPI™ system.

Figure 10. Dekati® Low Pressure Impactor for gravimetric measurements. DLPI assembled on the left, and partly disassembled on the right.

2. Particle real-time mass size distributions

The primary data measured with the ELPI™ from the 12 different impactor stages is current distribution. This current distribution is then converted in ELPIVI software to particle number size distribution (*Marjamäki et. al. 2000, Virtanen et.al. 2001*), which is the calibrated concentration value. The ELPI™ has been calibrated for correct particle number concentration but other type of distributions can be calculated using this data making certain assumptions of the particle size, shape and density. The particle density value can be inserted in the software if it is known, and then used in the calculations. However, in some cases the mass data measured with ELPI™ real-time measurement can be higher than the gravimetric result. For example if the sample humidity is high, and particles are hygroscopic the ELPI™ will measure the particles with the particle-bound water (since the measurement is in real-time), and therefore a higher mass concentration results. More details on the calculation of the ELPI™ mass results can be found in technical notes ELPI Calculation and Unidealities in ELPI mass measurement.

Conclusions

ELPI™ instrument can be used in three different ways to get information on the particle number size distribution and concentration, particle mass size distribution and concentration and particle charge distribution. In inhalation aerosol studies the ELPI™ can be used to measure all these parameters and thus gain information on many different particle characteristics. The instrument has successfully been applied to measurements of e.g. MDIs, DPIs and nebulisers, and can be used to measure any type of pharmaceutical aerosols that are in the operating size range of the ELPI™ – 7nm -10µm.

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For further information on the ELPI, please contact support@dekati.fi