Case Study:
Cleaning Validation at API production units

Description of the approach (recommended settings)

HPTLC offers an inexpensive and time-saving way to control industrial cleaning. The following describes the procedure.

Specifications for cleaning validation:

1. Choice of cleaning solvent

The solubility of the manufactured products in different solvents is investigated. Solvents of low toxicity are preferred like acetone, ethanol, 2-propanol or acetic acid.

2. MACO calculation

The calculation takes into account the therapeutic daily dose (TDD) of active ingredients (AIs) as well as a factor of security depending on the route of administration of the product B.

$$MACO = \frac{TDD\ A\ x\ 10^6}{Sf\ x\ TDD\ B}$$

- MACO in mg/kg (maximum allowable carryover)
- TDD A in mg/kg (cleaned product)
- TDD B in mg/kg (following product)
- Safety factor (Sf) depending on the route of administration

Route of administration	Sf
Use externally	10
Oral product	100
Injectable product	1000

3. Calculation of specified concentration

Corresponds to the concentration of product tolerated in the last rinsing solvent. It is define on the basis of MACO, the batch size and the volume of cleaning solvent.

$$Specification = \frac{MACO\ x\ Sb}{V}$$

- Specification in mg/L
- MACO in mg/kg
- Size of product lot (Sb, in kg) manufactured after cleaning (product B)
- Volume (V, in L) of the last solvent rinsing to clean

Validation and control of industrial cleanings:

1. Sample Preparation

Industrial installations are cleaned by successive fillings with cleaning solvent. The cleaning is completed by a mechanical action. The sample (250 mL) is directly levied at the time of the emptying of the equipment and used for HPTLC without any sample preparation. The specification (maximum acceptable concentration) is calculated on the basis of the MACO and the volume of the equipment.

2. Sample Application

In the ADC 2 with chamber saturation (usually for 3 min), migration distance 50 mm from lower plate edge. Prior to development, plates are conditioned at 33 % relative humidity for 5 min using a saturated solution of magnesium chloride. The mobile phase depends on the method selected due to the different polarities of the compounds.

3. Chromatography

Bandwise with Automatic TLC Sampler (ATS 4), 15 tracks, band length 8 mm, track distance 11.4 mm, distance from the side 20 mm, distance from lower edge 8 mm, usual application volumes between 0.5 and 2 µL for standard solutions and between 0.5 and 100 µL for samples solutions according to the respective specification.

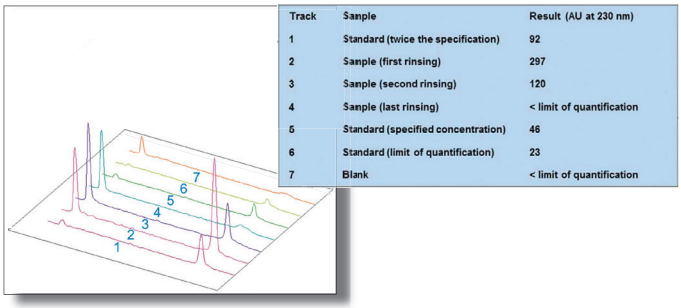
4. Densitometry

TLC Scanner 4 with visionCATS/winCATS software, spectra recording from 200 to 700 nm for identification, quantification by absorption measurement at the specific wavelength for each target analyte, slit dimension 5.00 x 0.45 mm, scanning speed 20 mm/s, polynomial calibration by peak height.

5. Results

The conformity of a cleaning is assessed on two criteria: 1) The last 3 rinses are controlled to verify the effectiveness of the cleaning. This efficiency is assessed and evident by the gradual decrease of the residual product concentration in the different samples 2) In the last rinse, the residual product concentration in the sample has to be below the respective specification.

Each sequence consists of three samples per cleaning, one sample of solvent of “white” rinse (the solvent blank used for the last rinsing) and standards. Three standard levels are used to facilitate the assessment, i.e. the identification of the target substances (the AIs) and evaluation of compliance: one standard level corresponding to: the limit of quantification (T3) the specification (T2) twice the specification (T1).



Track	Sample	Result (AU at 230 nm)
1	Standard (twice the specification)	92
2	Sample (first rinsing)	297
3	Sample (second rinsing)	120
4	Sample (last rinsing)	< limit of quantification
5	Standard (specified concentration)	46
6	Standard (limit of quantification)	23
7	Blank	< limit of quantification