Development of Chemical Reference Substances

Qualis

by
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Outline

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Introduction

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Chemical Reference Substance

Is an authenticated, uniform material that is intended for use in specified chemical and physical test, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use*

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Primary Chemical Reference Substance

- Is one that widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance.*

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Secondary Reference Substance

Is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

The extent of characterization and testing may be less than primary chemical reference substance*

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Reference Material

- Material, that is sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

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Certified Reference Material

- Is a reference material characterized by a metrological valid procedure for one or more specified properties, accompanied by a reference material certificated that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

Protocol

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- Intended of use;
- References;
- Chemical profile of the substance;
- Characterization of the substances;
- Purity profile;
- Assay profile;
- Stability profile;
- Storage recommendation;
- Other information (MSDS); and
- Proposed label and packaging.

Intended use

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- Calibration of measurement system;
- Assessment of a measurement procedures;
- Assigning values to other material; and
- Quality Control

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Intended use

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- Infrared spectrophotometry for identification and qualitative proposes;
- Quantitative methods based on ultraviolet (UV) absorption spectrophotometry
- Quantitative methods based on development of a color and measurement of its intensity, whether by instrumental or by visual comparison.
- Methods based on chromatographic separation for identification or qualitative proposes.

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Intended use

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- Quantitative methods (including automated methods) based on other separation techniques that depend on partition of the substances to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that occasionally vary from laboratory to laboratory
- Quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationship
- Assay methods based on measurement of optical rotation, and
- Methods that might require a chemical reference substance consisting of fixed ratio of known compound (for example, cis/trans isomers spike samples).

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Characterization

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- The intended use of reference material depend on what the Testing parameter performed to characterized it.
- Testing parameter choose to characterized should bring lots of information needed for the substance to be suitable as a reference material.

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Testing parameter

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✓Identification
✓Purity or impurity:
- Related substances
- Degradation products,
- Solvent residue,
- Volatile substances,
- Water content,
- Other impurities (Metals, acids, Alkalis etc.)

✓Assay

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Identification

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- Infrared spectrophotometer or FTIR
- UV-Vis Spectrophotometer
- Color test, development of color after mix with specific reagents.
- Polarimeter or refractometer.
- Melting range or melting point.
- NMR
- LC or TLC followed with color test or other test.

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Identification

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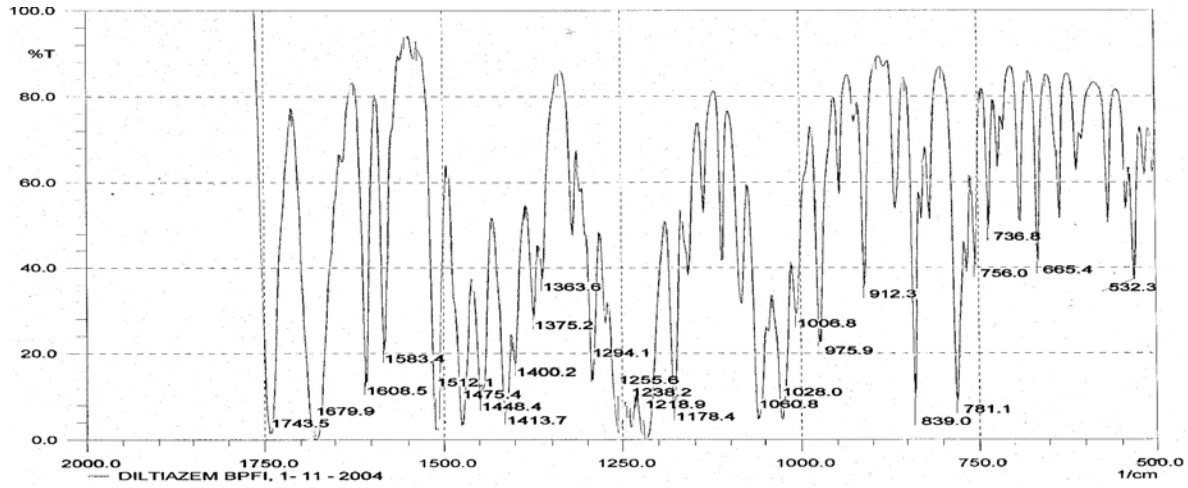
IR Spectrometer or FTIR



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Identification

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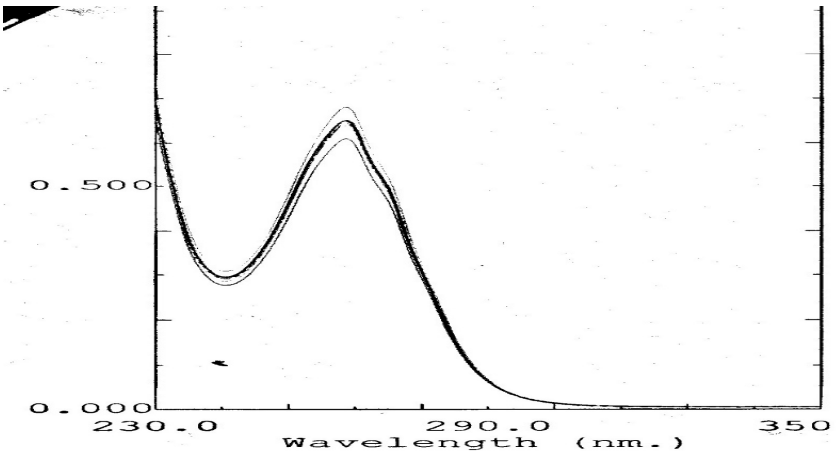
Spectrophotometer UV-Vis



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Identification

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Polarimeter or refractometer

Polarizes and refractive index is a very typical test of a substance. So it can be used as an identification of substance.

Identification

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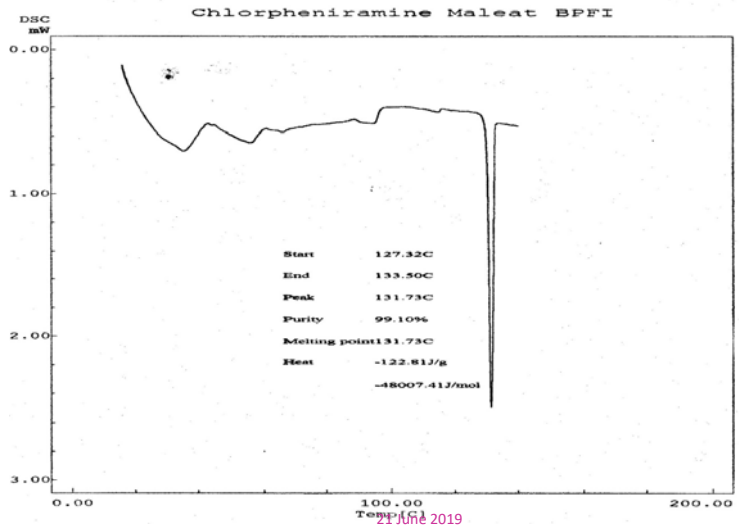
Melting point or melting range



Purity profile

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Impurity chemical reference substances:

- Organic impurity formed at the beginning or during production process or storage. The impurity could be found in the raw material, solvent, catalysator or as result of degradation product.
- Inorganic impurity is a result from synthetically process, include from reagents, catalysator, heavy metal and inorganics salt.
- Residual solvents: Organic or inorganic solvents that were added during synthetically production.

Purity test

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- Identification of related substances (HPLC, TLC, PSA, GCMS or LCMS).
- Identification of impurity (HPLC, TLC, UV, IR)
- Limit test of specific substances or salt/alkali/acid
- Determination of residual solvents (GC)
- Water content (Karl Fischer or gravimetric)
- Lost on drying or determination of volatile substances (oven heating or GC).

Purity test

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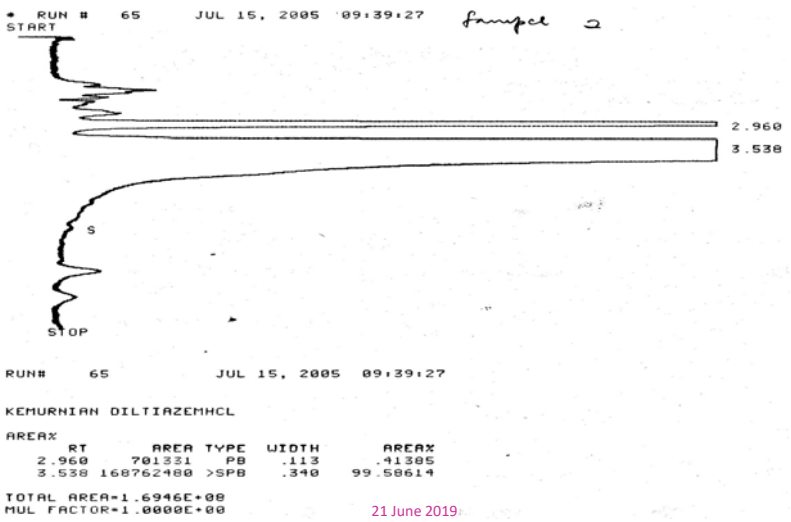
♠ Related substances (HPLC)



Purity test

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♠ Related substances (TLC)

By comparation with reference substances

- Quantitatively determination
- Should have the reference substances
- Mostly expensive and difficult to get

By relative normalization

- It is semi-quantitative, as it is only as a prediction of the number of impurity (related substances), and could be conformed by MS
- It is more practicable and less expensive

Purity test

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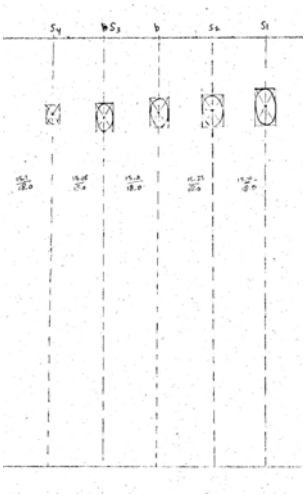
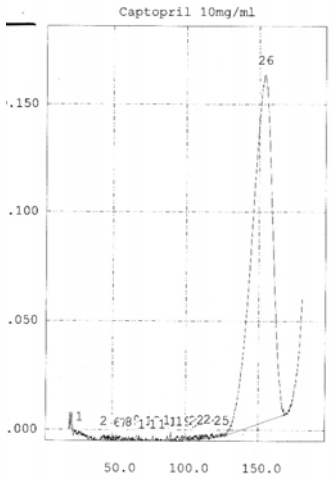
♠ **Related substances (TLC)**





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Purity test

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Phase solubility Analysis:

- Determination of the impurity by preparing solution of supersaturated substances in several series, and take the same volume of solution, dry them and weight.
- If the substances is pure the residue will be the same weight, the different is the weight of soluble impurity/ies.

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Assay

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- Titrimetric determination
- Spectrophotometric UV-Vis (λ_{max})
- Spectrophotometric IR/FTIR (λ_{max})
- Liquid Chromatography (RT and area/ high)
- Gas Chromatography (RT and area/ high)

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Reporting

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- ✓ Report of analysis result is prepared based testing performed.
- ✓ If several assay were done by several different of method, the content of analyte should be calculate by its method.
- ✓ Some reference substances producer established the certificate on request.
- ✓ There could be a signature of the responsible person on the establishment of the reference substances or none.

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Packaging and Storage

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- Transparent or amber vial/bottle/ampule others.
- Well closed, vacuum, inert gas.
- Rubber closed and aluminum cup.
- Tightly label and clear information.
- Store in room or ambient temperature, cold storage (5-8^{o}C), freeze (<0^{o}C).
- Protect from light, dry place (over silica gel).
- Specific handling system (for high toxic, sensitive).

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Labeling

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Information the label:

Name of the substance;
Control No or code no. or batch no.;
Assay;
Content of each package;
Name of the institution, address, email and phone number, and

Other important information e.g. expired date, storage, handling, specific instruction, warning.

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Instruction of use

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- Dry it at 105°C for 2-6 hours, before use;
- Dry it at 60°C vacuum for 6 hours, before use;
- Dry it over silica gel for 12 hours, before use;
- Determine water content, before use;
- Do not dry before use.

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Stability testing

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- To establish the expire date of the Chemical reference substances, a stability testing should be performed during the analysis, storage with appropriate temperature and accelerated study with extreme condition.
- Monitoring stability of the RS should be done periodically depend on the stability report of the bulk producer (if any) other information.

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Re-analysis

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Re-analysis should be done when the RS just arrive both from Industrial agency of RS established institution, the test should be done:

1. Identification: by color test, IR Spectrometer or TLC or LC, and
2. Water content or loss on drying (especially when the RS received after 1 month transferred).

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Re-analysis

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Re analysis should be done for confirmation that the substance still valid to be used, especially when the container has been opened for 6 months or more. The re-test could be done by using one or more of this methods:

- ✓ Purity test (TLC, LC, GC)
- ✓ Determination of the substances
- ✓ Water content or loss on drying.

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Challenges

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- Limited CRS product;
- Limited of dedicated labs;
- Limited source of the raw material or the substances;
- No information about stability profile;
- Expensive; and
- Limited distribution (Immigration, law).

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Summary

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1. Chemical Reference substance is very important for validation method of QC program;
2. Establishment of in house reference substances will bring lots of benefit for QC laboratories;
3. Parameter development for analysis proposed CRS should cover all aspect of chemical and physical testing to characterized the substances.
4. Packaging and storage of the CRS should based on stability and sensitivity profile of the substances.
5. Certificated of analysis could attached to the distributed substances or not.

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References

1. World Health Organization, "*WHO General Guideline for The Establishment, Maintenance, and Distribution of Chemical Reference Substances*" in WHO Expert committee on specification for pharmaceutical preparation, WHO Technical Report Series 885, Thirty-fifth report. WHO, Geneva 1999. Annex 3, page 29-44
2. ILAC-G12:2000, *Guidelines for the Requirements for the Competence of Reference Material Producers*
3. ISO Guide 17034:2016 *General requirements for the competence of reference material producers.*

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Question ??