Determination of solubility and dissolution rate of nanomaterials in water and relevant synthetic biological media

with support from
G4N & NH

in support of a
new OECD Test Guideline

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+ associated for RR: FORTH (GR), IIT (IT), KRISS (KR), NIOH (ZA), URMC (US), Canada, Japan, UoB (UK)

International Workshop
on
Gap Analysis and Data Requirement
to support
OECD Test Guideline and Guidance Document Development

Thursday 5th of November 2020 Session 1

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 885931

Consensus building
on round robin criteria
-
Discussion

Solubility / Dissolution Setups

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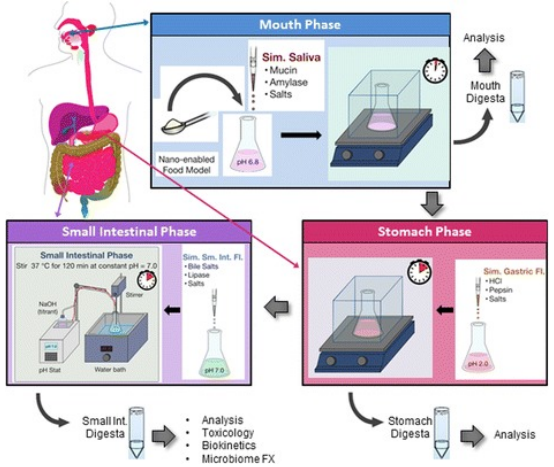
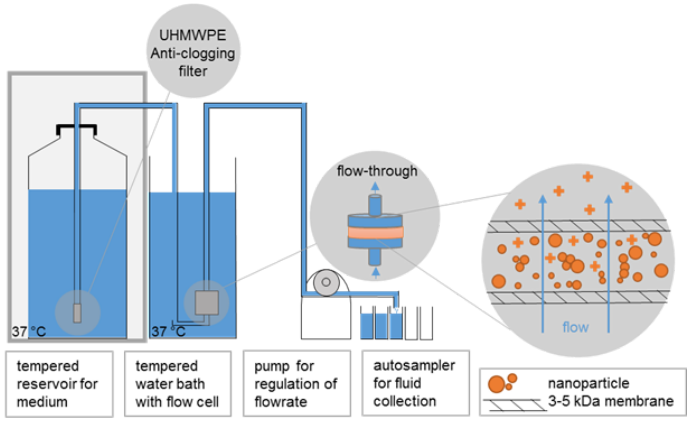
Sequential GIT solubility
BfR & BASF
(transferred from BAM to BfR)



Simulates oral uptake

saliva → stomach → intestine:
pH6.4 – pH2.0 – pH7.5
All by ISO 19738

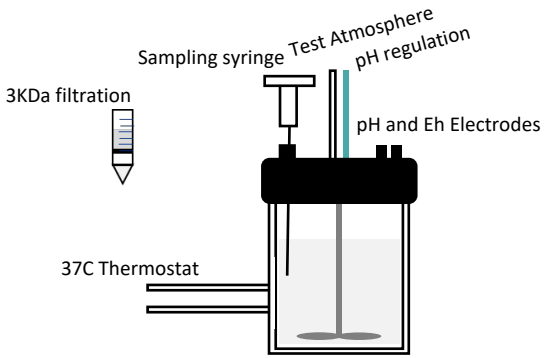
Continous Flow System (CFS)
BASF
(transfered in PATROLS to KRISS)



Simulates pulmonary uptake and hours-to-years biodissolution

„Gambles“, pH7.4
„PSF“ pH4.5 ISO19057

Atmosphere-Temperature-pH-controlled Stirred Batch Reactor (ATempH SBR)
NRCWE (transfered to KRISS)



Simulates short-term (e.g.24 hour) biodissolution

„Gambles“, pH7.4
„PSF“, pH4.5 ISO19057
Planned for simple GIT testing

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Solubility / Dissolution finalising SOPs, validation and harmonisation

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Sequential GIT solubility
BfR & BASF
(transferred from BAM to BfR)

- Draft SOP (under revision at NRCWE)
- Draft Guidance document (Tips related to SOP), incl. sample prep from separation particles vs. ions, peptide digestion, matrix-matched ICPMS calibration (Ce, Zn, Al, Ti)
- Preparation for intra-laboratory ring trials, finalizing all documentation
- Finalizing raw data calculations (ZnO)

Continous Flow System (CFS)
BASF
(transfered in PATROLS to KRISS)

- Draft SOP is revised in PATROLS
- Justified adjustable parameters:
  - Predictable influence of fluid volume flow and valid range. (Keller, Peijnenburg et al 2020)
  - Lysosomal simulant media: Out of 5 media identified 3 as valid (ISTEC+BASF, to be submitted)
- More than 100 NM tested.
- Benchmark materials identified

Atmosphere-Temperature-pH-controlled Stirred Batch Reactor (ATempH SBR)
NRCWE (transfered to KRISS)

Validation (OECD materials, 3x3 data)

- Al_2O_3 , TiO_2 (NM-104), ZnO (NM-110, NM-111, NM-113), SiO_2 (NM-200), CeO_2 (NM-212), Bentonite (NM-600)
- Finalized, data analysis on-going Manuscript in preparation

Proof-of-concept: PATROLS materials

- 12 identical materials were now tested in 2 identical fluids by CFS (BASF) and ATempH SBR (NRCWE)

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Consensus-building on round-robin criteria for solubility and dissolution testing of NM in pure water and biologically relevant media

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- ***Potential measurands for solubility and dissolution testing***
  - What are the essential measurands, which should one be reported?
    - Discussed requested more comprehensive reporting incl the most robust measurand:
    - Ion concentration at each sampling time point
    - Evaluation thereof as fitted halftime + evaluation as rate (via surface area, shape)
  - Mandatory testing of control materials for quick / partial / very slow dissolution?
    - Consensus on need for control (benchmark) materials.
  - Is it possible to achieve a harmonized selection for the three protocols?
    - Yes: uncoated forms of ZnO and TiO_2 favored. Potentially NM110 and NM101 from JRC repository.
  - What are appropriate criteria for acceptance (expected criteria given via validation process)?
    - Guidance needed for regulators to assess results that originate from different labs & methods
    - Control materials contribute to acceptance

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Discussion points: solubility / dissolution testing

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- ***Harmonization of reporting formats/templates for data gathering***

  - What are appropriate criteria for reporting?
  - What reporting formats should be used allowing documentation and accessibility afterwards?

  Suggestion to use established templates from EU project GRACIOUS as basis

  - GRACIOUS template "in NANoREG style" was developed by IIT (oral), UNIVIE (env.), BASF (inhalation) dissolution tests, with IDEA (enanomapper import to databases)
    - Discussion requested more comprehensive reporting incl the most robust measurand:
    - Ion concentration at each sampling time point (to be added to GRACIOUS template)
    - Evaluation thereof as fitted halftime + evaluation as rate (via surface area, shape) (already given)

  - Further points of discussion: reporting of composition of medium, temperature, stirring (type, intensity). Consideration of size distribution, agglomeration/aggregation, surface and shape of particles over time as it enters into evaluation of the rate (not in the simpler evaluations)

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Announcement of the round robin testing for solubility and dissolution

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- Planned time lines for round robin (Jan 2021 -> June 2021); 5-6 Test materials

  - January 2021: →SOP distribution and clarifications
  - February 2021: →Distribution of test materials
  - March 2021: → Expected start of testing
  - June 2021: → Expected completion of testing

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