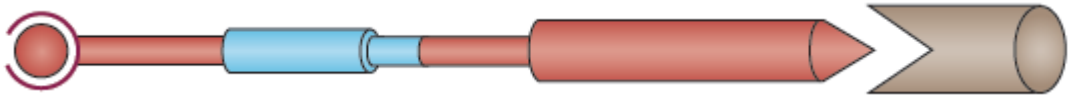
Quality Control of Radiopharmaceuticals

吳世彥

迴旋加速器中心運轉員

Radiopharmaceutcials (RPs)

- = radioisotopes + pharmaceucal



radioisotope link pharmaceutical target

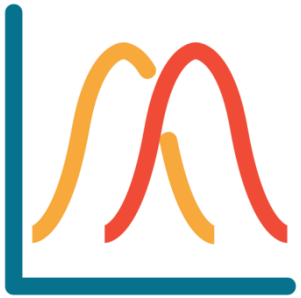
- essential for nuclear medicine practice
- 95% for diagnosis
- quality control to ensure the radiological and pharmaceutical safety and efficacy in accordance with the specifications laid-down

Quality Control of radiopharmaceuticals

- *Physicochemical Tests*

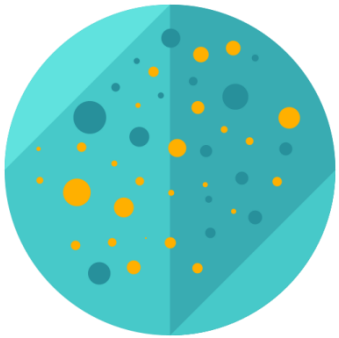
physical characteristic

pH and ionic strength

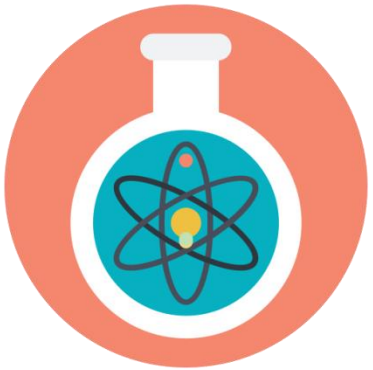


chemical purity

radiochemical purity



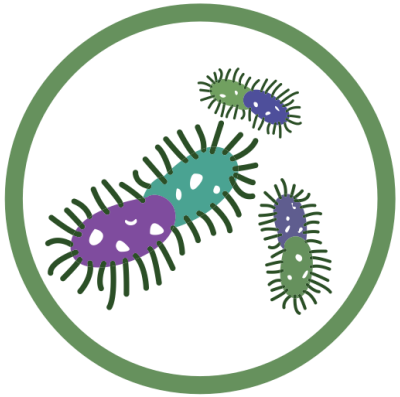
specific activity



radionuclidic purity

Quality Control of radiopharmaceuticals

- *Biological Tests*



Sterility

apyrogenicity

physical characteristic

Color/appearance

Most radiotracers

colorless/clear

^{99m}Tc-sulfur colloid

amber/slight turbid

^{99m}Tc-microsphere

yellowish/turbid

Any change from the original colour and clarity

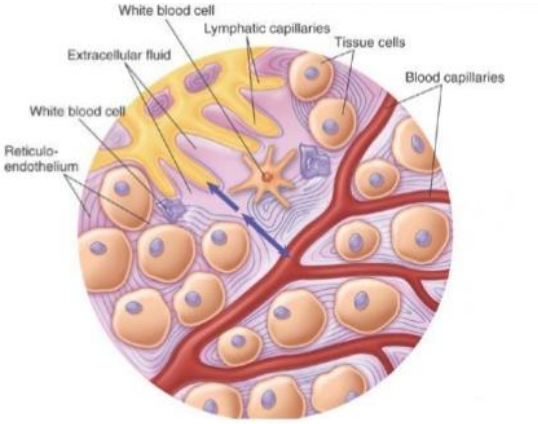
- changes in the RPs that would alter its biologic behaviour.

Particle size of RPs suitable for a given purpose

- ^{99m}Tc sulfur colloid
  - # **0.1-1 µm** for liver and spleen imaging
  - # larger aggregated particles

↑

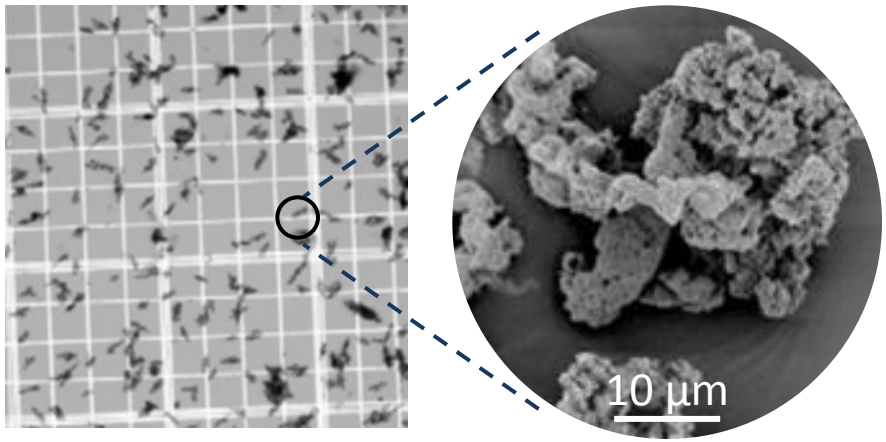
deposit in the lungs



reticuloendothelial system
in the liver

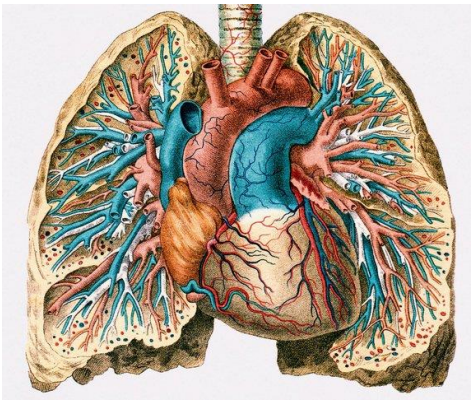
Particle size of RPs suitable for a given purpose

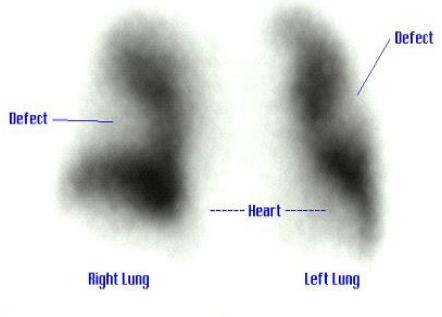
- ^{99m}Tc-MAA



10-90 µm

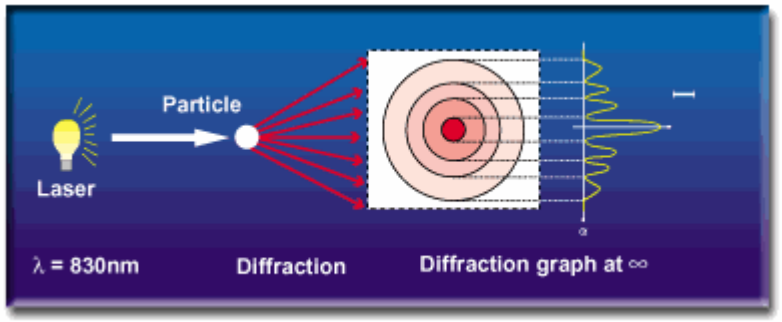
^{99m}Tc-macroaggregated albumin

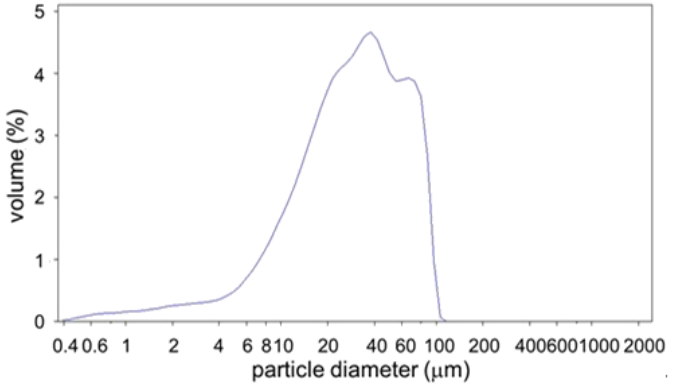




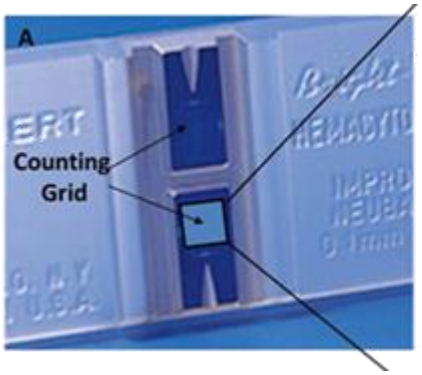
Particle size analysis

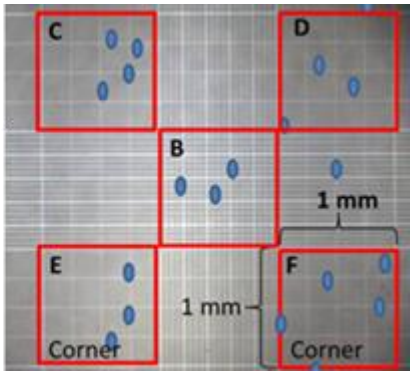
- laser diffraction particle size analyzer





- microscope





pH and ionic strength

pH

- an appropriate pH for stability and integrity of RPs

$$pH = \log \frac{1}{[H^+]} = -\log[H^+]$$

  - using a pH meter or pH paper to measure regularly
  - ideal pH: 7.4 (pH of blood)
  - the range of pH that can be tolerated : 5.5-8

  because of the high buffer capacity of the blood

pH

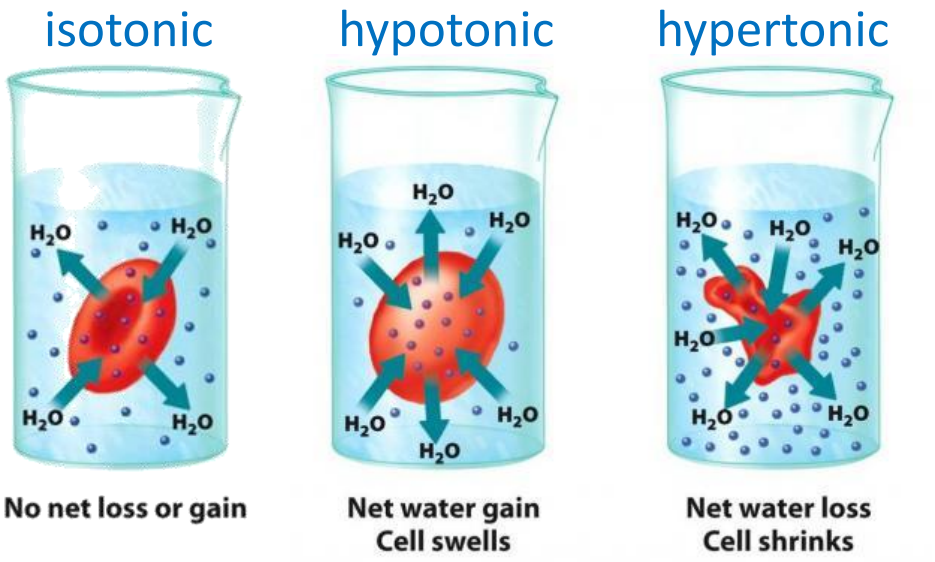
- Na*I solution: maintain alkaline to prevent sublimation of iodine

- $^{111}InCl_3$: maintain acidic to avoid the formation of $^{111}In(OH)_3$

$$InCl_3 \rightarrow In(OH)_3$$

Isotonicity and ionic strength

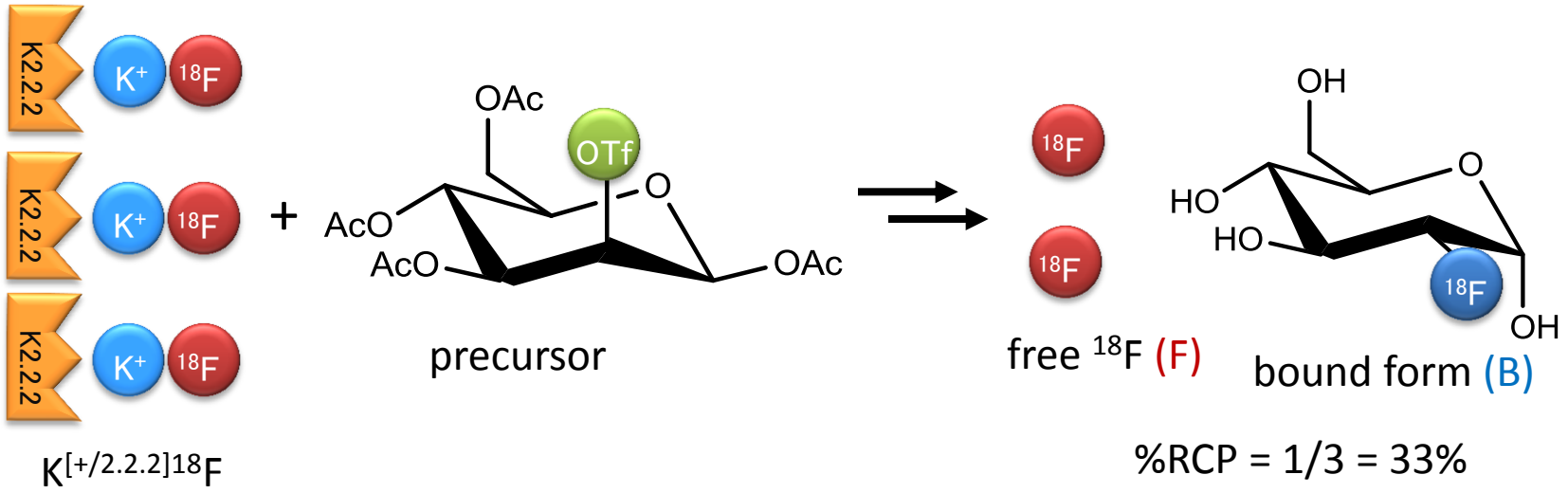
- Appropriate ionic strength is important
  - # suitable for human administration
  - # for providing both stability and physiologic compatibility of RPs
  - # obtained by adding a proper acid, alkali or electrolyte



An osmometer for initial validation study and for periodic re-check

radiochemical purity

Radiochemical purity (RCP)



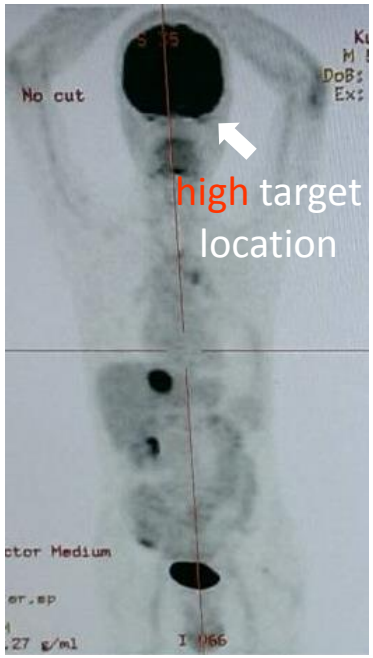
$K^{[+/2.2.2]18}F$

%RCP = 1/3 = 33%

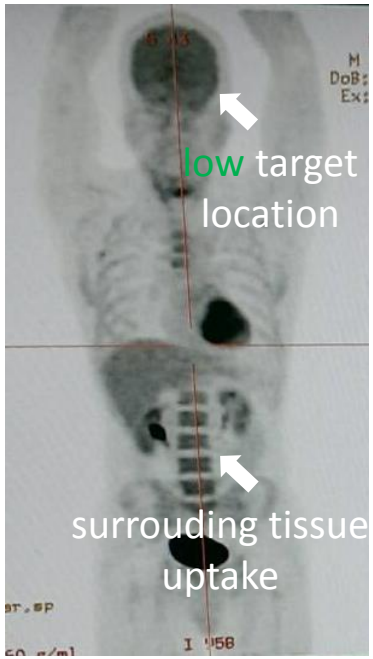
- $\%RCP = \dfrac{\text{radioactivity of (B)}}{\text{radioactivity of (B) + (F)}} \times 100\%$

Radiochemical purity (RCP)

high RCP



low RCP



Radiotracer with low RCP

- low target location
- high surrounding tissue uptake

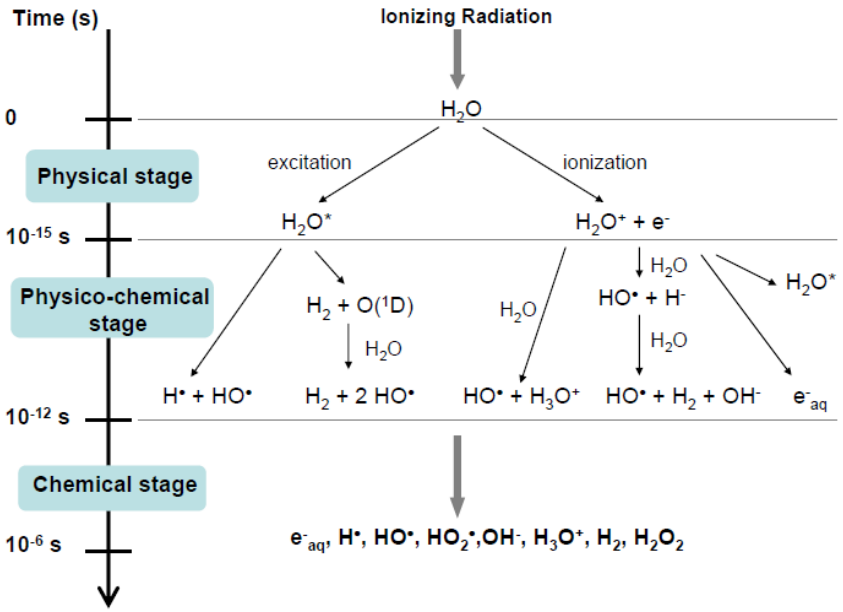
- poor-quality image
- unnecessary radiation dose to the patient

Sources of radiochemical impurities

- free radionuclide
- temperature, pH or light
- the presence of an oxidizing or reducing agent
- radiolysis

Radiation degradation (radiolysis)

- Radiation degradation (radiolysis)



1. **Two hydroxyl radical can combine to form hydrogen peroxide (H_2O_2) that is converted back to water by the organelle called the peroxisome:**

$$OH^\bullet + OH^\bullet \longrightarrow H_2O_2$$

hydrogen peroxide

2. **The hydrogen radical and the hydroxyl radical can combine to form water:**

$$H^\bullet + OH^\bullet \longrightarrow H_2O$$

3. **The hydrogen ion and hydroxyl ion can combine to form water:**

$$H^+ + OH^- \longrightarrow H_2O$$

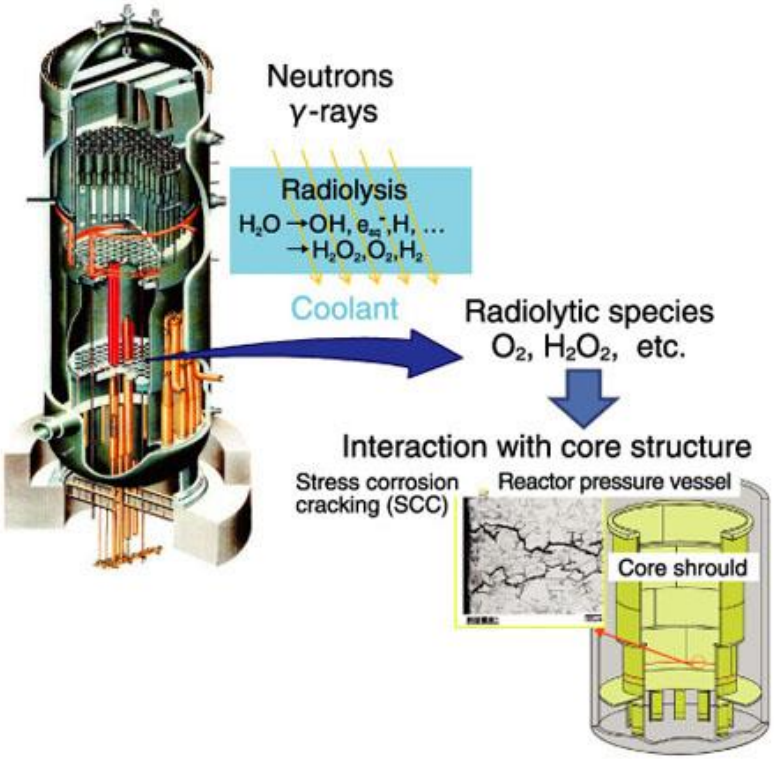
4. **The hydrogen free radical can combine with molecular oxygen to form a highly reactive hydroperoxyl radical which continues the chain of radical damage to biomolecules:**

$$H^\bullet + O_2 \longrightarrow HO_2^\bullet$$

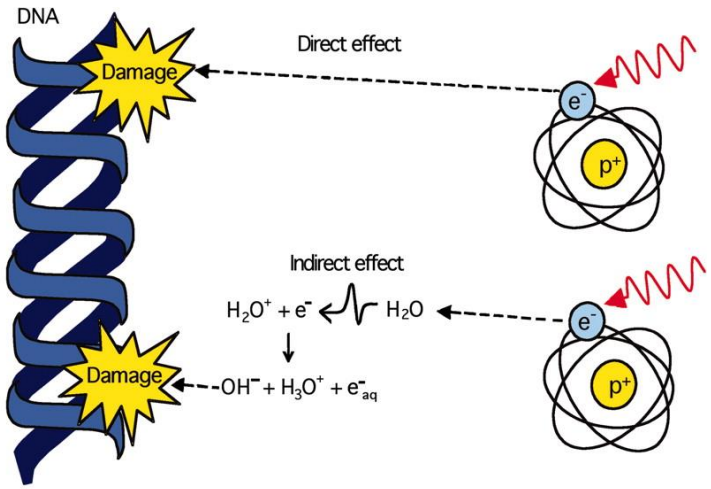
hydroperoxyl radical

https://www.ceessentials.net/article3.html
Water 2011, 3, 235-253

damage by radiolysis



Water radiolysis and corrosion in a reactor core



Ionizing radiation induces direct DNA damage and indirect damage through the radiolysis of water.

Radiochemical purity (RCP)

- Radiation degradation depends on
  - the specific activity of the radioactive material
  - the type and energy of the emitted radiation

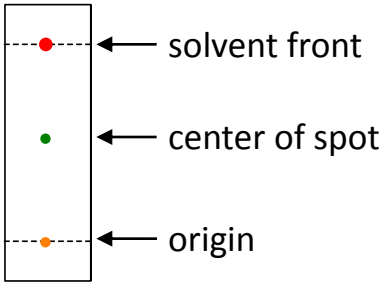
    alpha > beta > gamma
  - the half-life of the radionuclide

- To maintain the stability of RPs
  - lower specific activity
  - by adding ascorbic acid or $Na_2S_2O_3$
  - stored in the dark under refrigeration.

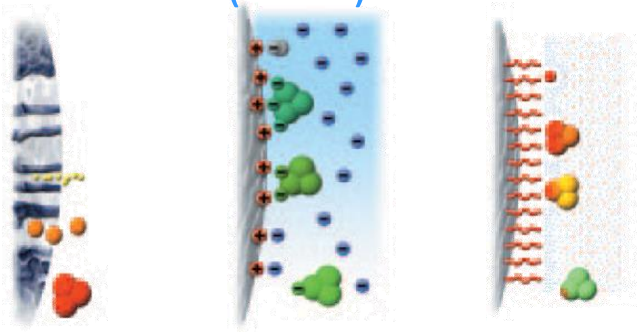
Radiochemical purity (RCP)

- Analytical methods for RCP

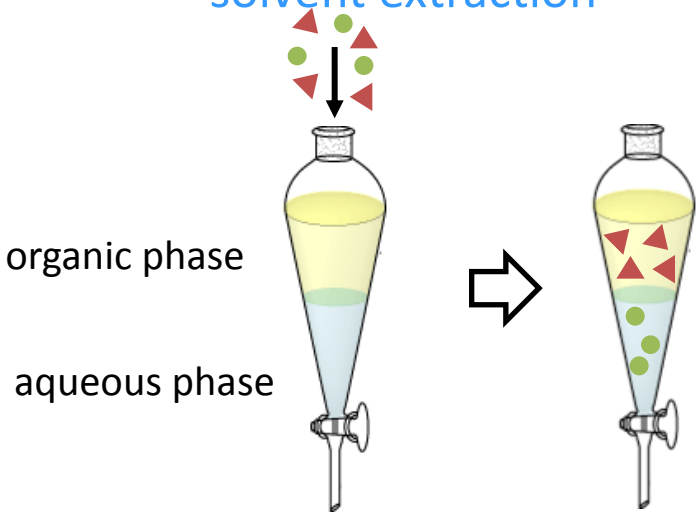
thin layer chromatography (TLC)



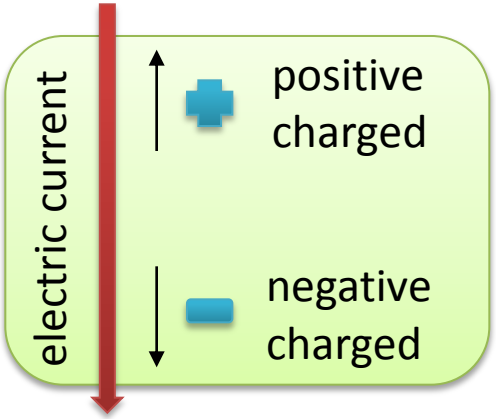
high-performance liquid chromatography (HPLC)



solvent extraction

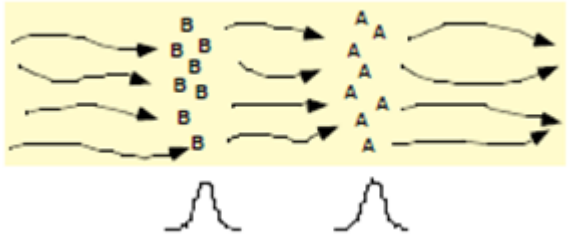


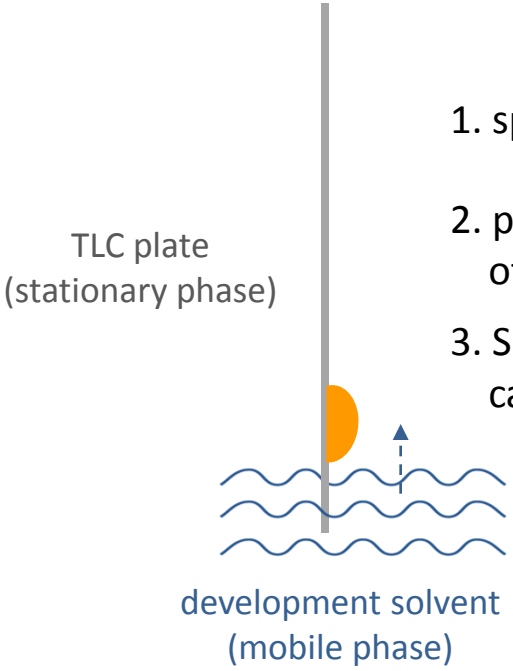
gel electrophoresis



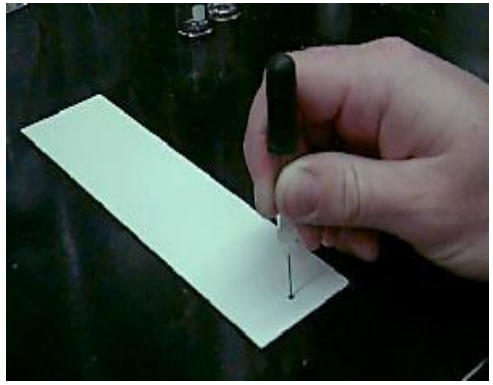
Radiochemical purity-analysis methods

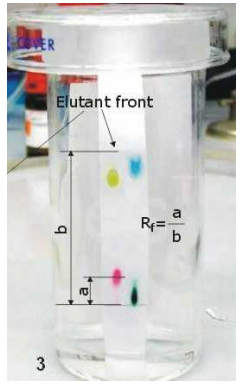
- Thin layer chromatography (TLC) is used to determine
  - # the number of components in a mixture
  - # the identity of compounds
  - # the purity of a compound



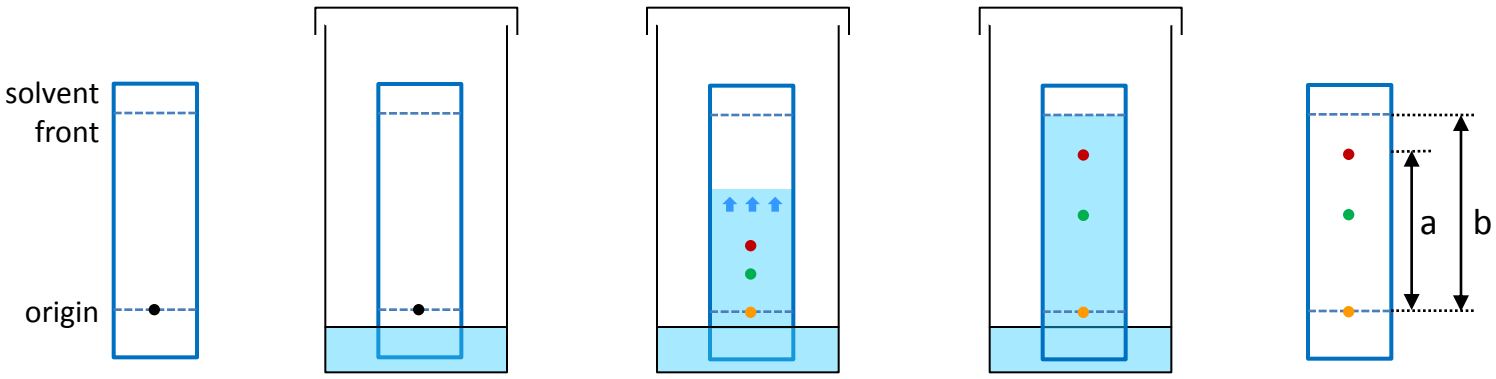


1. spot of sample to be analyzed
2. plate is placed into a pool of development solvent
3. Solvent rise up plate by capillary action





Radiochemical purity-analysis methods



$$\text{Retardation factor } (R_f) = \frac{\text{the distance traveled by the compound (a)}}{\text{the distance traveled by solvent front (b)}}$$

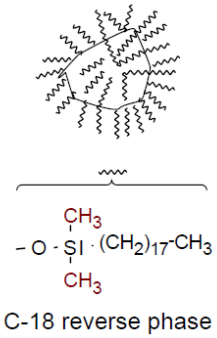
- Each radiochemical species travel a characteristic distance, and this is represented as the R_f value .
- R_f values can be used to aid in the identification of a substance by comparison to standards.

Radiochemical purity-analysis methods

- Stationary phase and mobile phase

Increasing polarity

Reverse phase (e.g. C-18)
Paper
Cellulose
Starch
Calcium sulfate
Silica gel
Magnesium oxide
Alumina
Activated carbon



C-18 reverse phase

Common stationary phases listed by increasing polarity

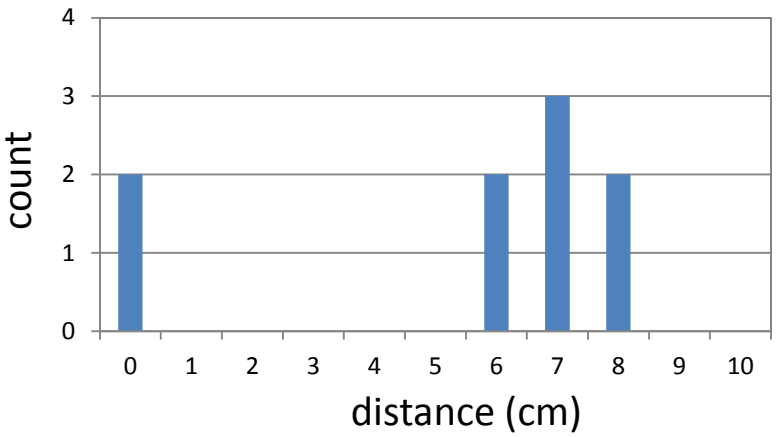
Increasing polarity

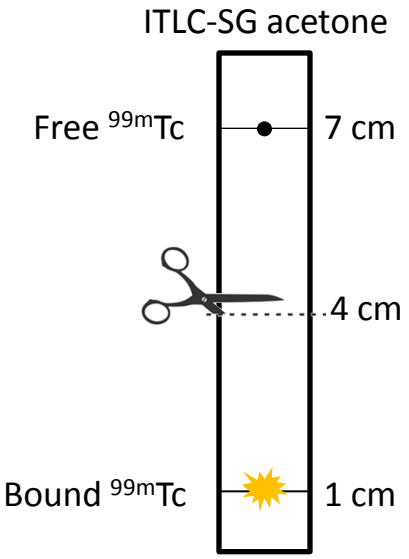
Petroleum ether
Hexane
Cyclohexane
Chloroform
Dichloromethane
Ether
Ethyl acetate
Acetone
Ethanol
Methanol
Water
Acetic acid

Common mobile phases listed by increasing polarity

Radiochemical purity-analysis methods

- The TLC plate is cut to determine the number of counts in each region representing specific radiochemical complex or complexes.
- These sections of the TLC plate are then counted individually using the appropriate instrumentation.
- After determination of the number of counts, calculations can be performed to determine the percentage bound and the percentage of radiochemical impurities.

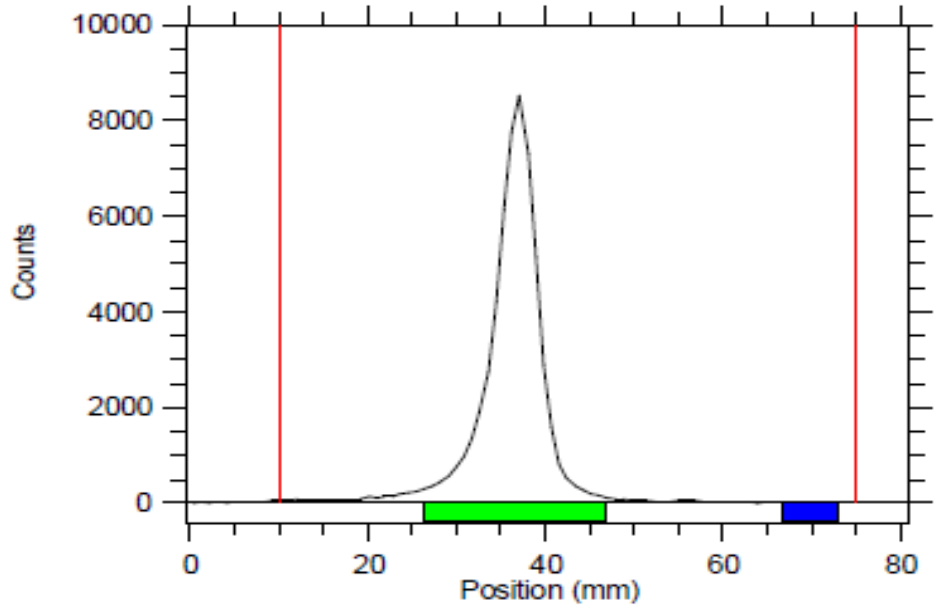




Radiochemical purity-analysis methods

- Alternatively, intact TLC plate can be scanned with a radiochromatogram scanner.

Reg	(mm) Start	(mm) Stop	(mm) Centroid	RF	Region Counts	Region CPM	% of Total	% of ROI
Rgn 1	26.3	47.0	36.4	0.406	55205.0	55205.0	94.49	100.00
Bkg 2	66.7	72.9	68.9	0.907				
1 Peaks					55205.0	55205.0	94.49	100.00



Radiochemical purity-analysis methods

- Instant thin layer chromatography (ITLC)
  - a rapid thin layer chromatographic assay developed to determine the labeling efficiency and the radiochemical purity of RPs
  - Stationary phase (adsorbent):

    Gelman ITLC-SG strips

    Whatman 3MM or 31ET paper
  - Mobile phase: solvent-saline, acetone (methyl ethyl ketone, butanone), etc.
  - With regard to ^{99m}Tc radiotracers, the three types of radiochemical components to be determined are as follows:

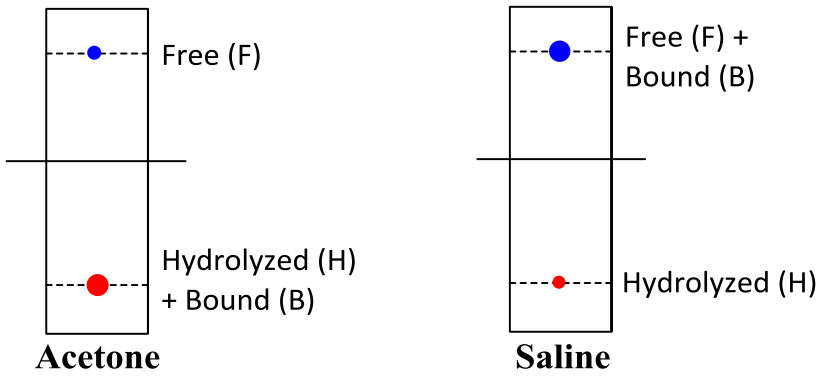
    (1) free ^{99m}Tc pertechnetate ($^{99m}TcO_4^-$)

    (2) hydrolyzed-reduced ^{99m}Tc (insoluble ^{99m}Tc dioxide and/or ^{99m}Tc tin colloid)

    (3) bound ^{99m}Tc to the ligand of interest.

Radiochemical purity-analysis methods

- Two chromatography systems (by using acetone and saline as mobile phases) was used to determined the radiochemical purity of ^{99m}Tc-RPs.



%Free ^{99m}Tc = F/[F+(H+B)] x 100, acetone was used as eluant

%Hydrolyzed ^{99m}Tc =H/[(F+B)+H] x100, saline was used as eluant

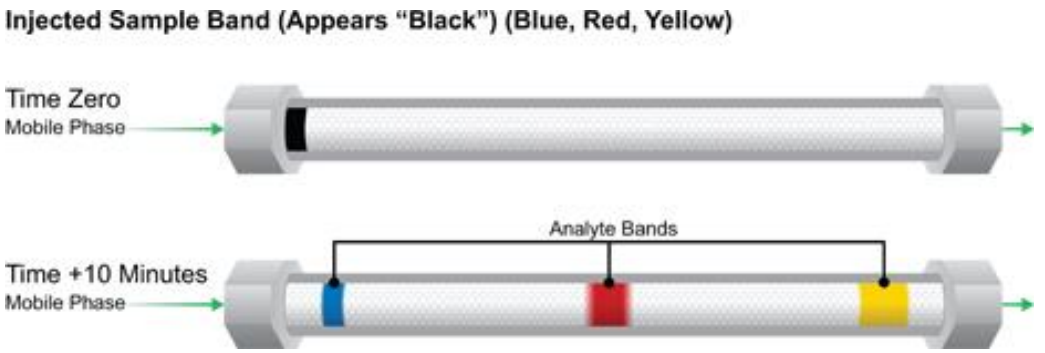
The radiochemical purity of %Bound ^{99m}Tc = 100% - [(F(%) + H(%)]

Radiochemical purity-analysis methods

- High Performance Liquid Chromatography (HPLC)
  - the most powerful chromatographic technique
  - high reproducibility, high speed, high resolution and versatility
  - detection limit: pico and feto gram amounts of sample
  - analytical and preparative application

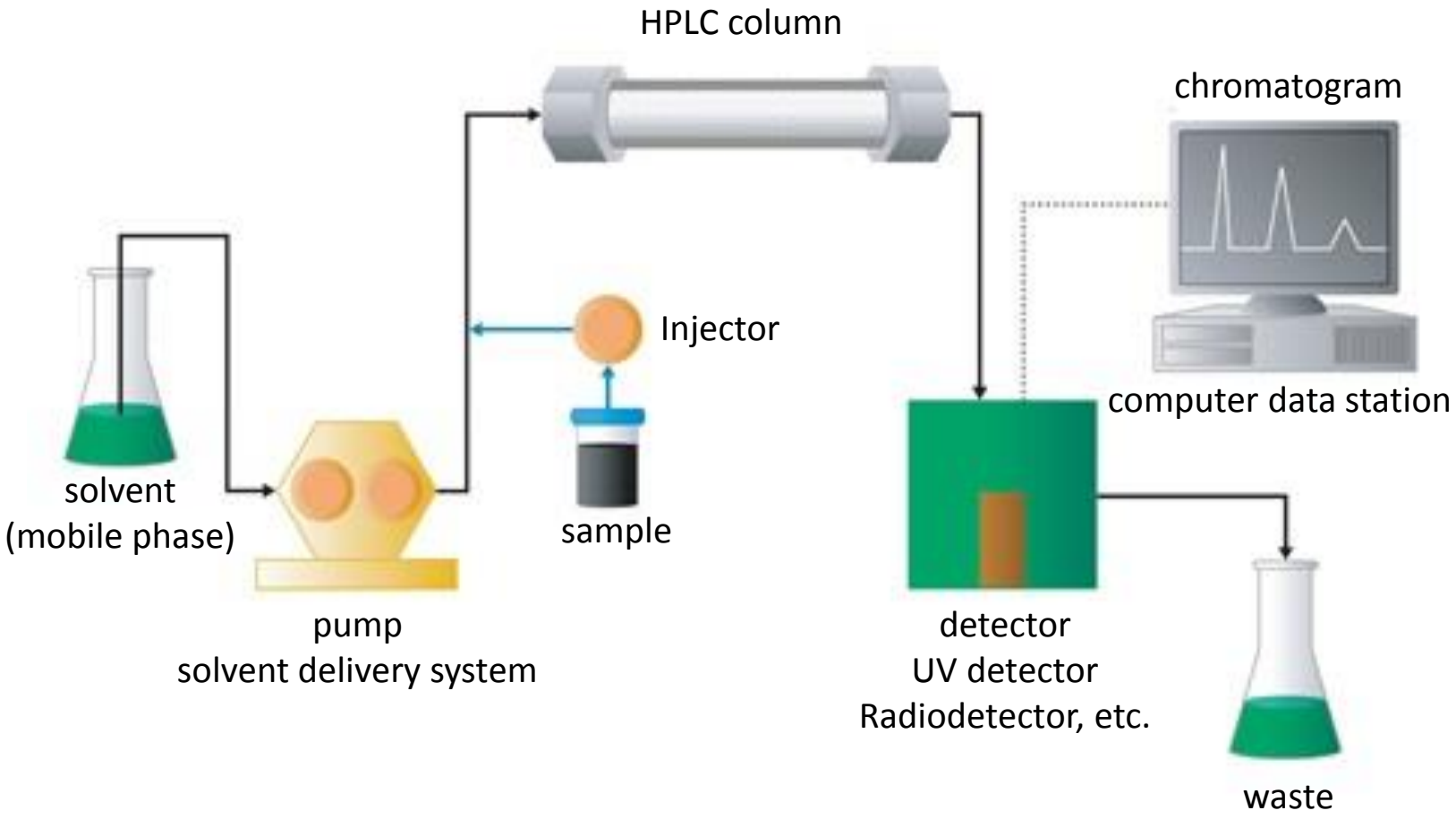
Radiochemical purity-analysis methods

- High Performance Liquid Chromatography (HPLC)
  - # Principle: Each component in the sample interacts slightly differently with the adsorbent material, causing different flow rates for the different components and leading to the separation of the components as they flow out the column.



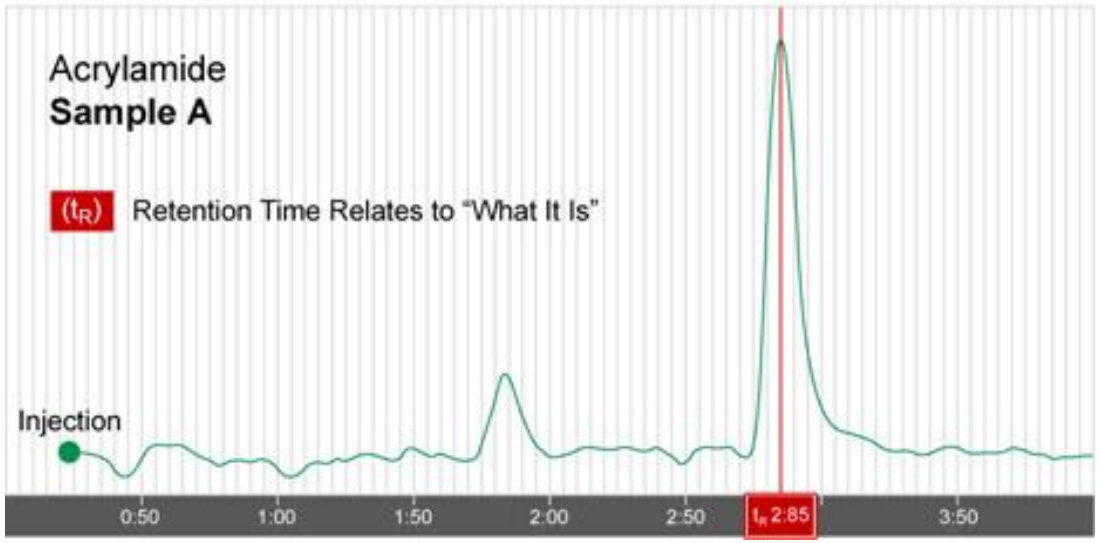
Radiochemical purity-analysis methods

- HPLC system



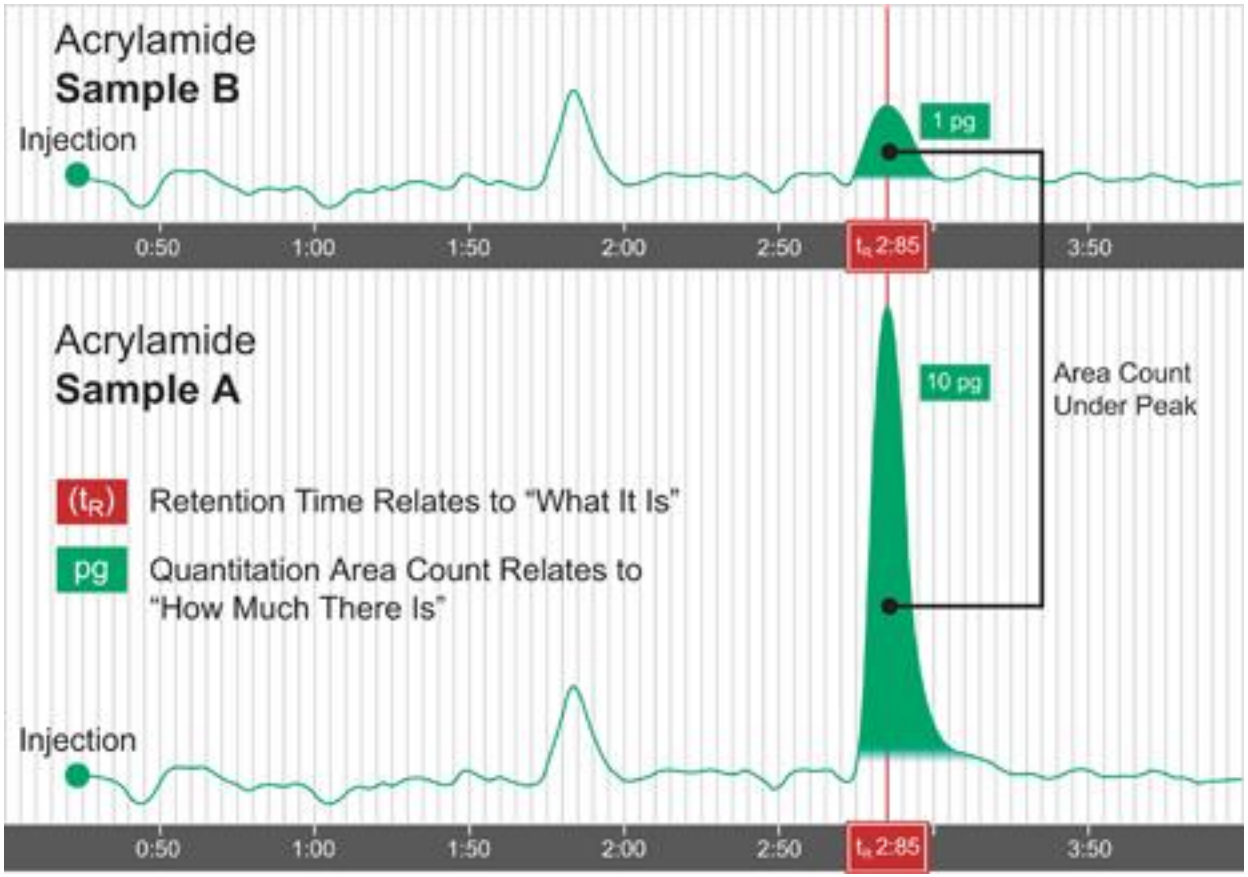
Radiochemical purity-analysis methods

- Identifying and quantitating compounds by HPLC
  - Retention time (t_R): Each elutes at a specific location, measured by the elapsed time between the moment of injection [time zero] and the time when the peak maximum elutes.
  - t_R of the same substance is always the same in the same condition .



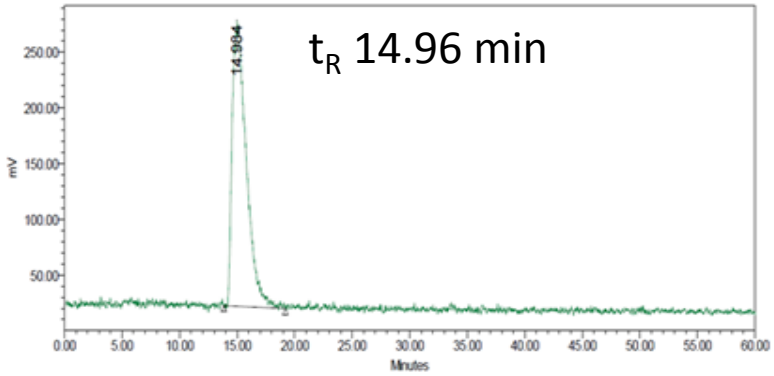
Radiochemical purity-analysis methods

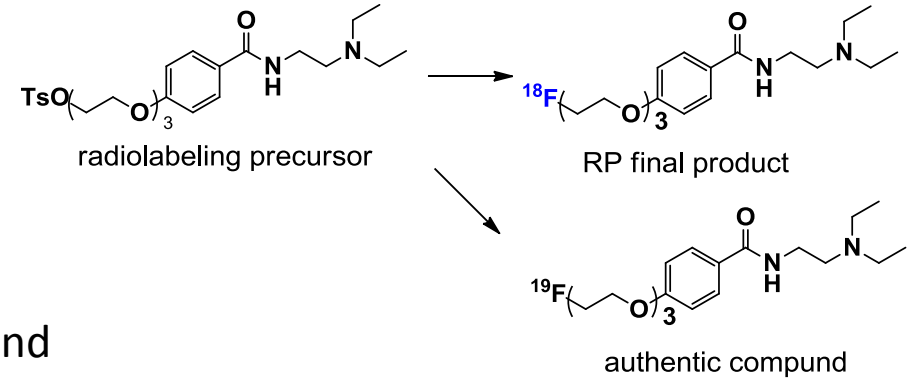
- Identifying and quantitating compounds by HPLC



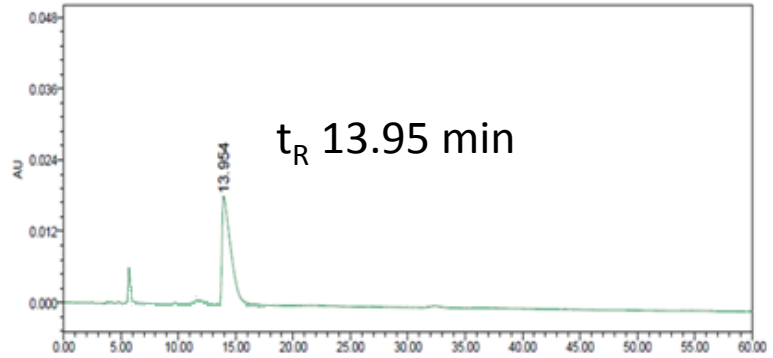
Radiochemical purity-analysis methods

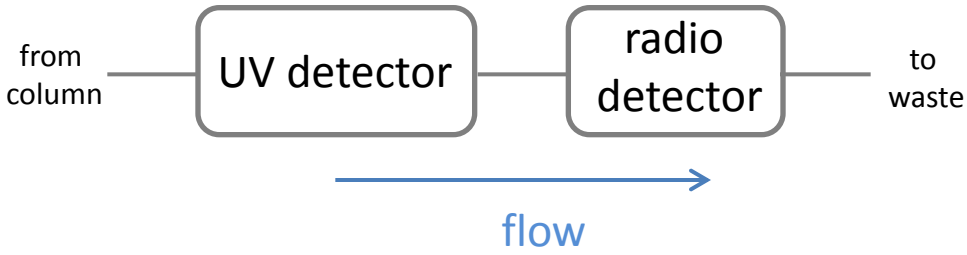
(A) Radio-chromatogram of RP final product





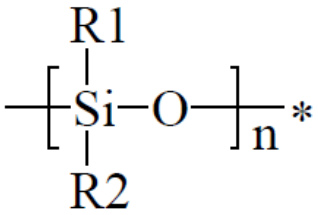
(B) UV-chromatogram of authentic compound





Radiochemical purity-analysis methods

- Types
  - Normal phase HPLC nonpolar solvent/polar column
  - Reverse phase polar solvent/nonpolar column

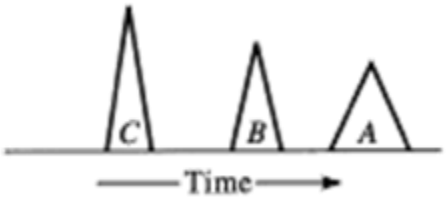


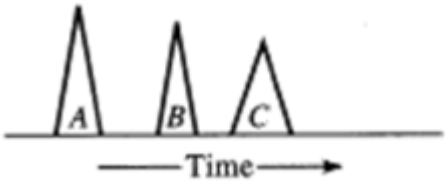
Normal phase R is cyano, diol, amino

Reversed phase R is C8 or C18 hydrocarbon

solute polarity: A > B > C

Normal phase HPLC	Reverse phase HPLC
low polarity mobile phase	high polarity mobile phase

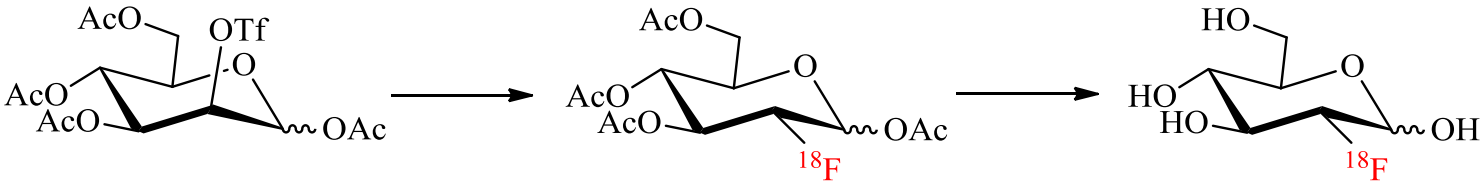




- Mobile phase
  - Isocratic elution: single mobile phase composition
  - Gradient elution: solvent polarity (composition) continuously varied

[^{18}F]FDG (2-[^{18}F]Fluoro-2-deoxy-D-glucose)

- The radiochemical purity of [^{18}F]FDG can be determined by radio-TLC and HPLC system equipped with UV detector and radioactive detector.



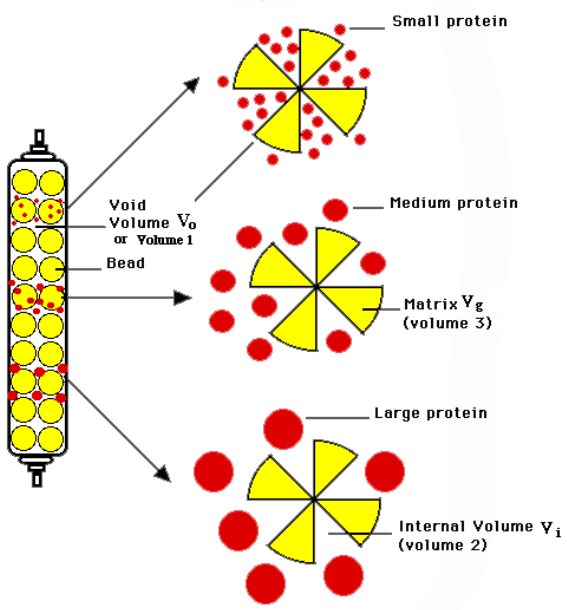
mannose triflate | Protected [^{18}F]FDG | [^{18}F]FDG

- TLC: silica plate; acetonitrile/water 95/5; (R_f = 0.4-0.5)
- HPLC: Lichrosorb-NH_2 column or carbohydrate column

  mobile phase: acetonitrile:water 85:15
- Ion exchange chromatography: Dionex PA 100 column, 0.1 M NaOH solution

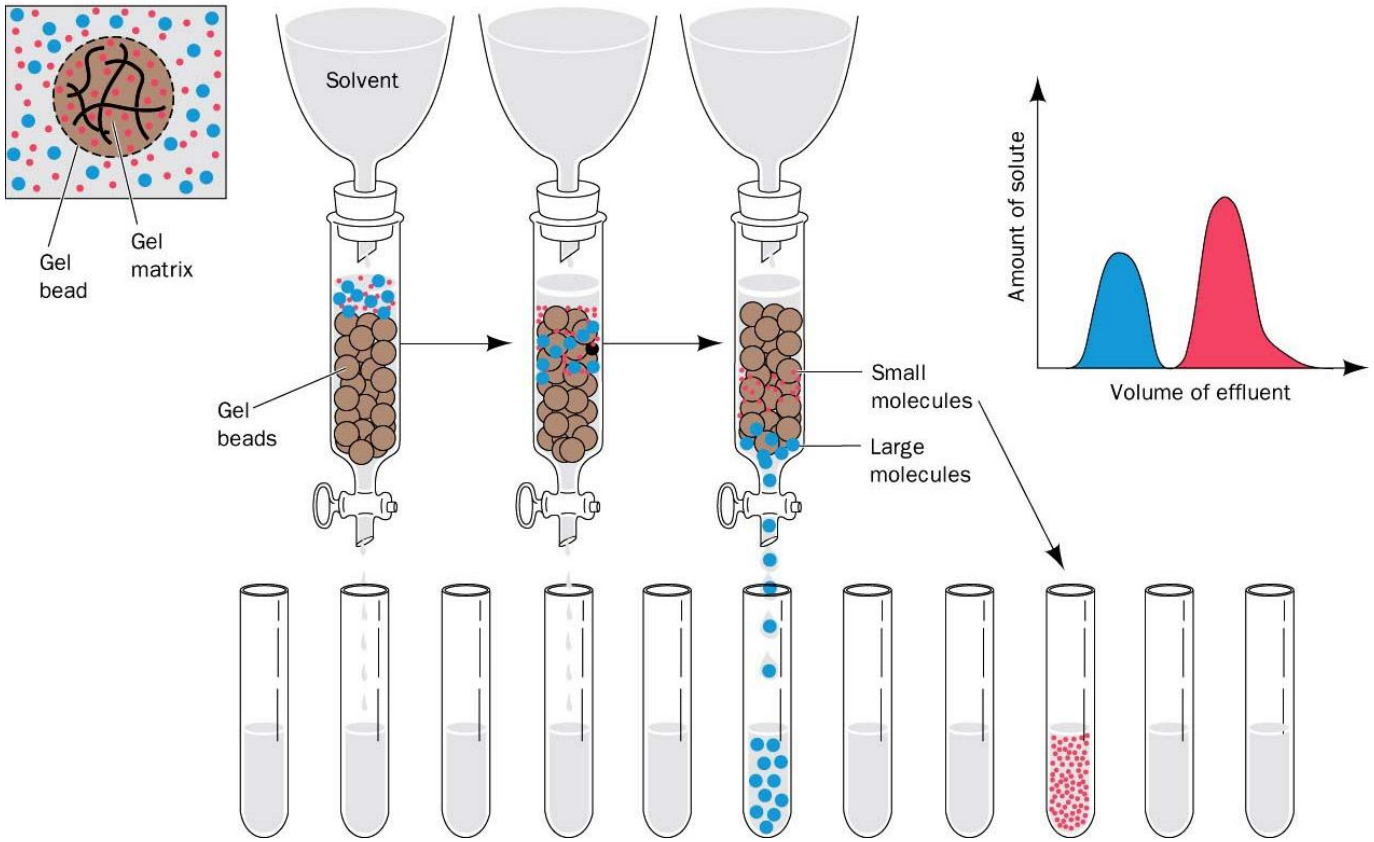
Radiochemical purity-analysis methods

- Gel permeation chromatography (size exclusion chromatography)
  - # Principle: separation is based upon molecular size and shape of the species in the sample.
  - # The chromatographic media used in this technique are porous, polymeric organic compounds with molecular sieving properties.
  - # sample:
    - Radiolabel proteins
    - ^{99m}Tc-radiopharmaceuticals

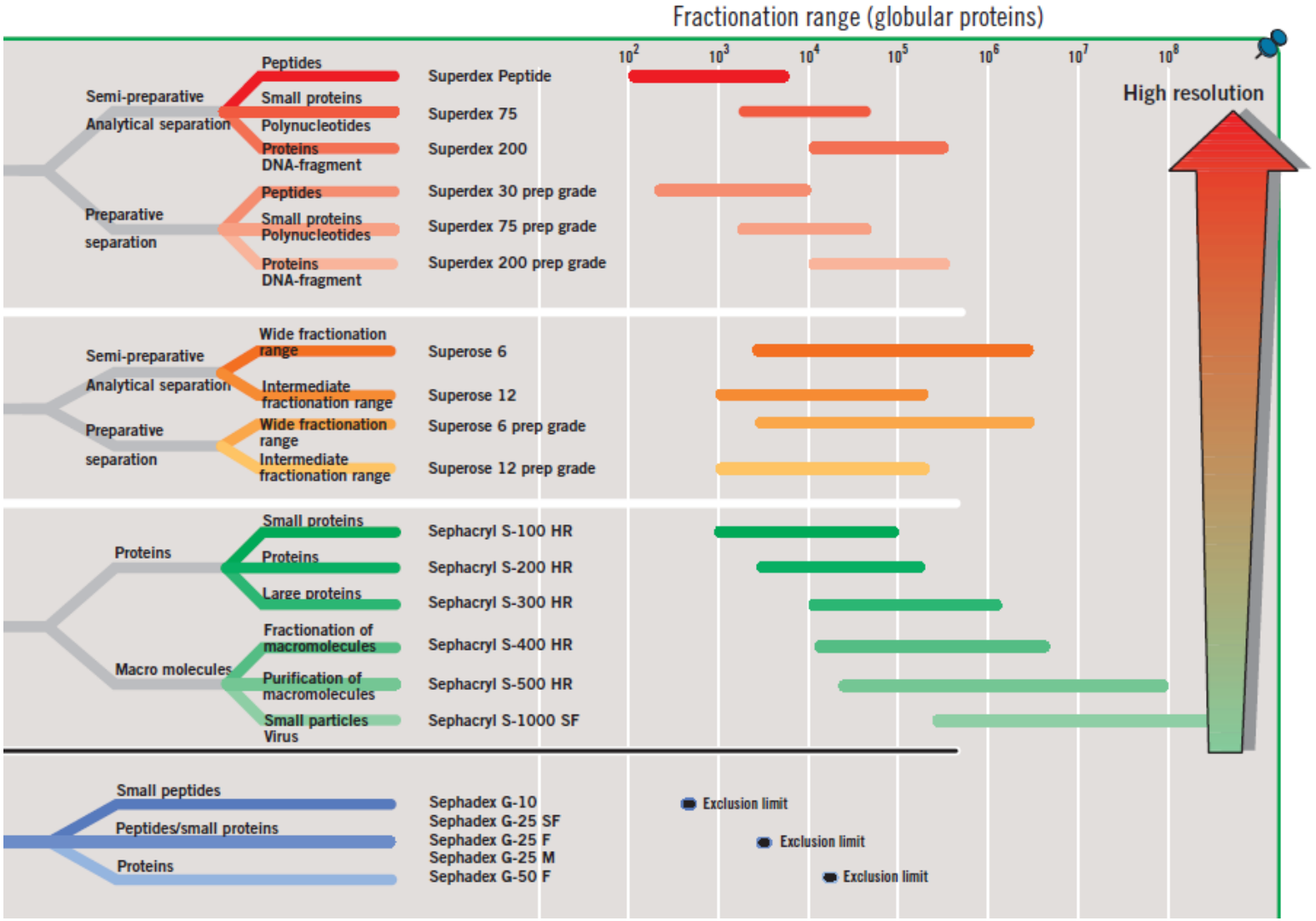


Radiochemical purity-analysis methods

- Gel permeation hromatography (size exclusion chromatography)

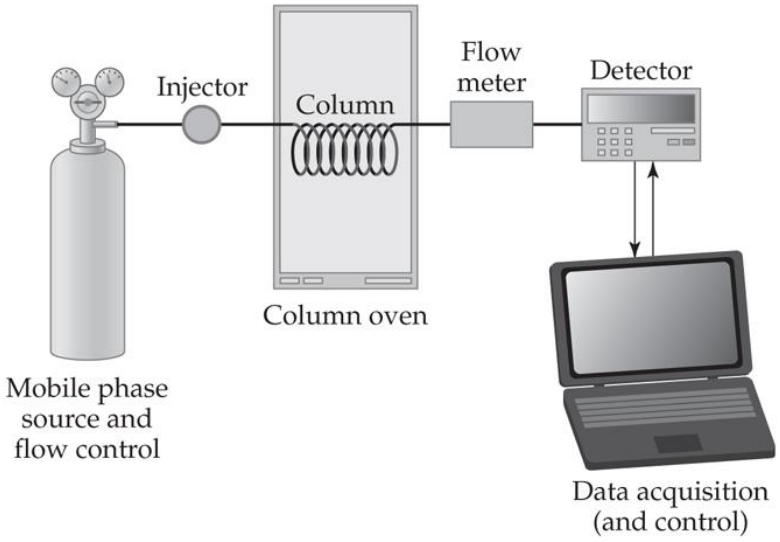


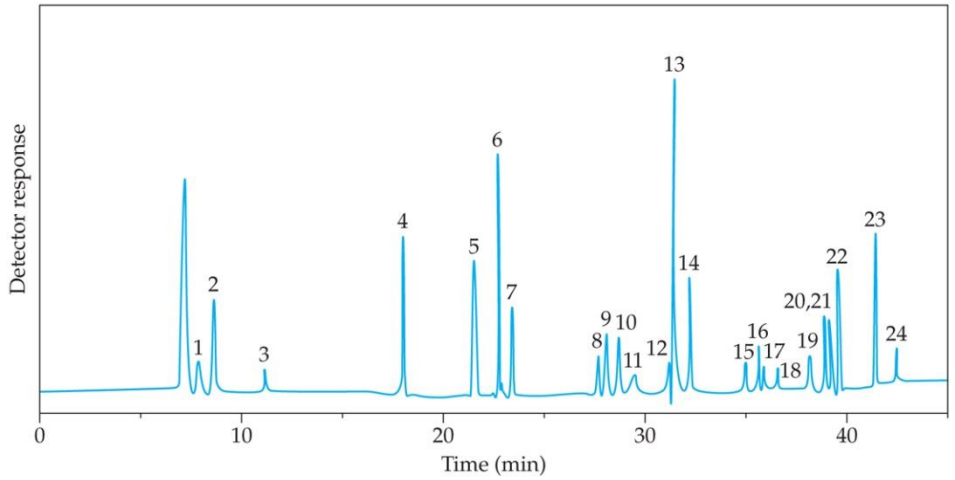
Radiochemical purity-analysis methods



Radiochemical purity-analysis methods

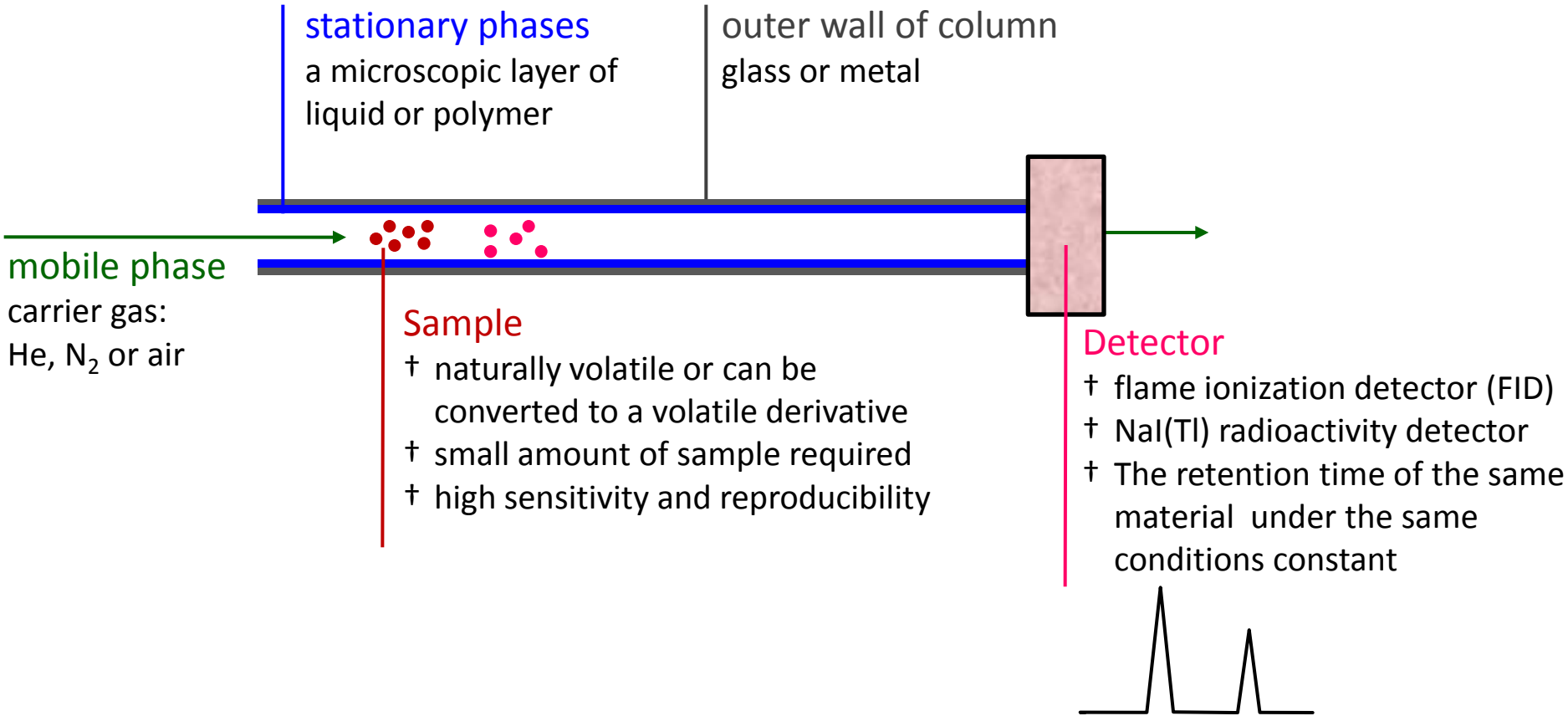
- Gas chromatography (GC)
  - # used to identify (compare to standards), separate, and quantify (use peak area) samples that can be vaporized without decomposition.





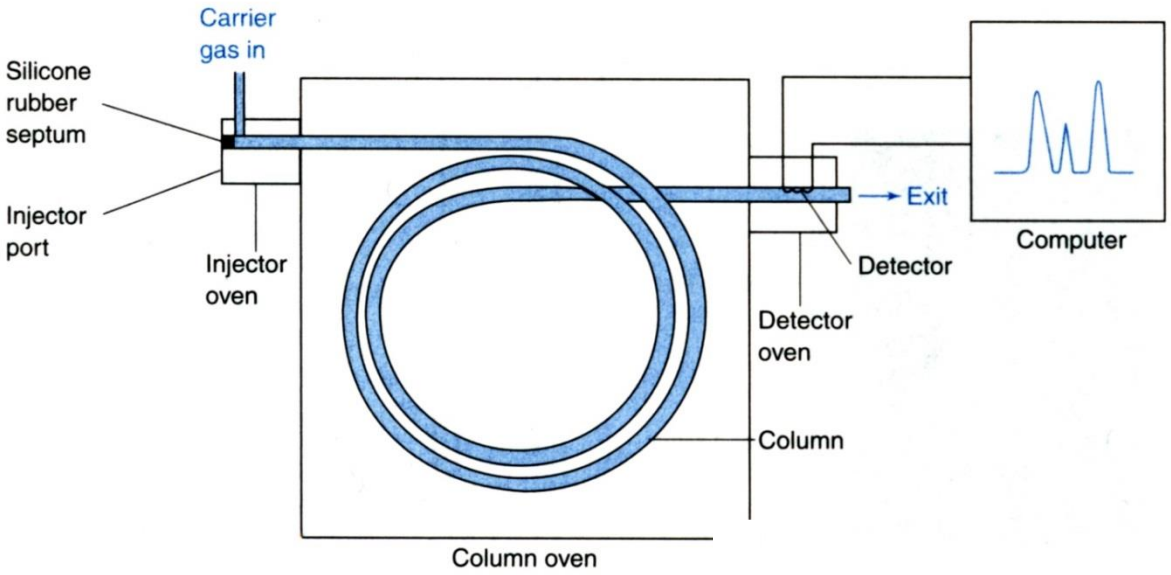
Radiochemical purity-analysis methods

- Gas chromatography (GC)



Radiochemical purity-analysis

- GC instruments and process
  - Volatile liquid or gas injected through septum into heated port
  - Sample rapidly evaporates and is pulled through the column with carrier gas
  - Column is heated to provide sufficient vapor pressure to elute analytes
  - Separated analytes flow through a heated detector for observation



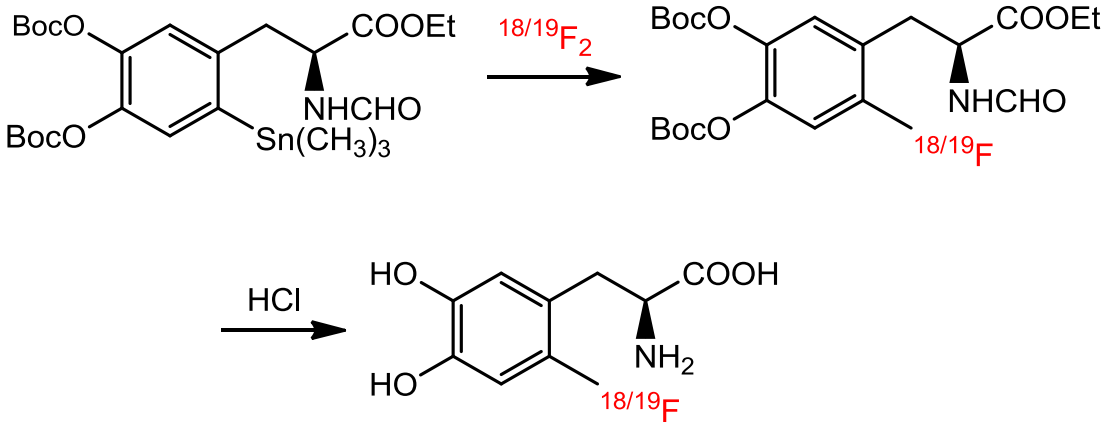
Radiochemical purity-analysis

- Gas chromatography – residual solvent
  - Identification and quantification of residual solvents (acetonitrile, ethanol, and perhaps DMSO) in the final solution may be performed with a gas chromatograph.
  - No more than 0.04% acetonitrile and 0.5% ethanol (based upon USP and Ph. Eur. specifications)

Specific activity

Specific activity (SA)

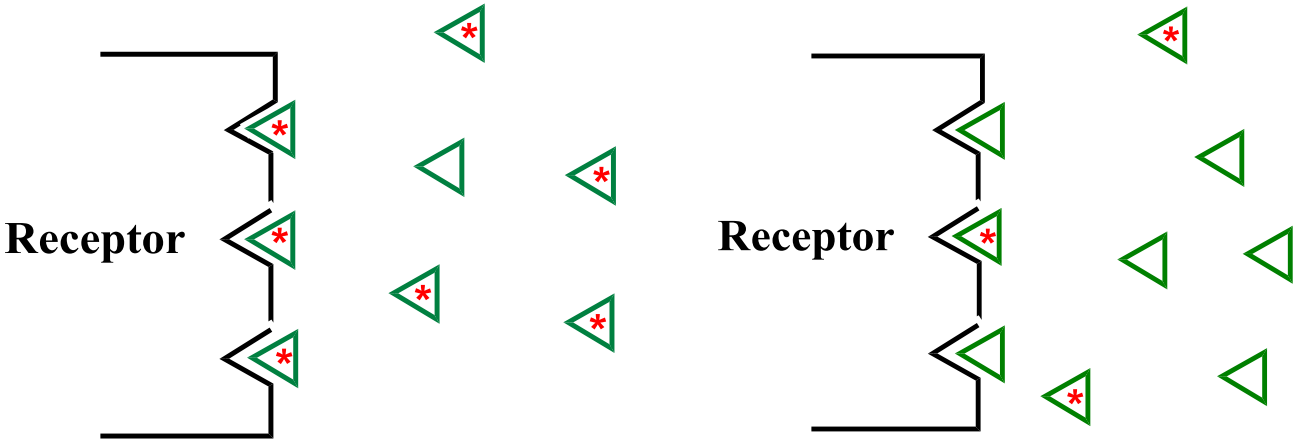
- defined as the quantity of radioactivity per unit mass (radioactive plus nonradioactive) of an element, molecule or a compound (including those of biological origin).
  - # should be stated on the label of/the individual dose with respect to a specified time.
  - # expressed as MBq/μmol, GBq/μmol or Ci/μmol



The specific activity of [^{18}F]FDOPA prepared using electrophilic [^{18}F]F_2 is ~1,700 mCi/mmol (USP 100 mCi/mmol), which is much lower that what is routinely obtained with radiotracers synthesized using nucleophilic [^{18}F]fluoride.

Specific activity (SA)

- Why is high specific activity important?



high specific activity

low specific activity

Specific activity (SA)

- Importance
  - Receptor ligands: requires a high SA, because the receptor concentration is low in general.
  - High SA is not necessary, if the similar materials are abundant in the body.

    Example: glucose derivatives, amino acids, fatty acids, nucleoside, etc.
  - However, high specific activity can cause more radiolysis in the labeled compound.
  - Particularly important when administering radiotracers that are toxic at low doses.

Specific activity (SA)

- Radioisotopes
  - # **^{11}C**:

    theoretical maximum specific activity: 9.2 x 10^6 Ci /mmol

    However, ^{11}C-labeled radiotracers show a rapid loss of SA over time

Ex.) every 3 min. → 10% of the radioactivity ↓

10% of the specific activity ↓

  - # **^{18}F ($^{18}F^-$)**:

    theoretical maximum value: 1.7 x 10^6 Ci/mmol

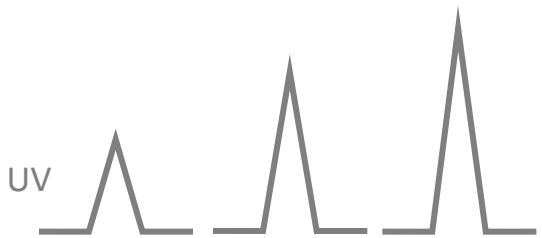
    actual value: 1 x 10^4 Ci/mmol

  - # **$^{18}F_2$**:

    due to F_2 carrier gas → low SA

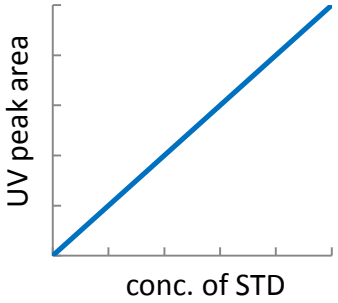
FDOPA QC-specific activity

1



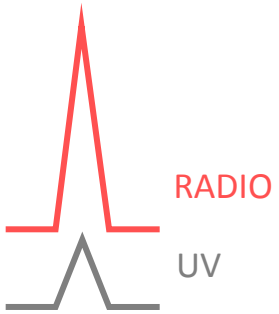
STD at different conc.

2



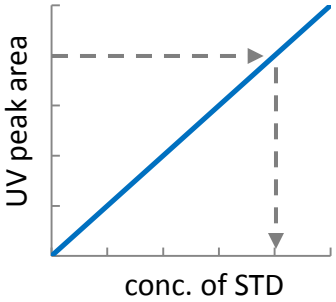
standard curve

3



analysis of ^{18}F-FDOPA

4



UV peak area

conc. of FDOPA (µg/mL)

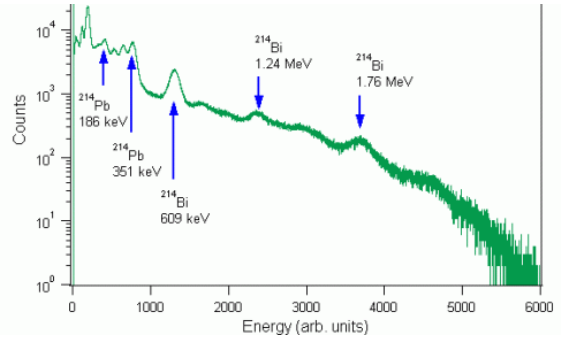
5

$$SA = \frac{\text{radioactivity (mCi/mL)}}{\text{conc. of FDOPA (µg/mL)}}$$

Radionuclidic purity

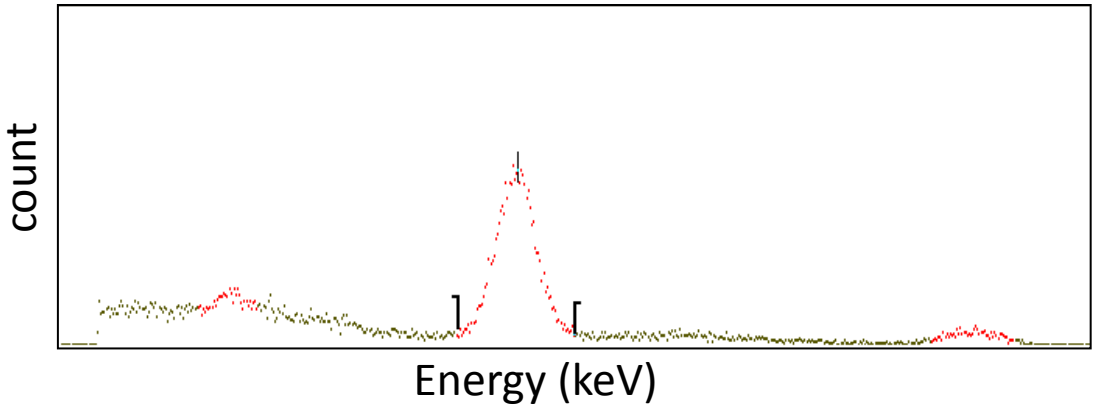
Radionuclidic purity

- the ratio of the stated radionuclide activity to the total radioactivity
- Necessity
  - # reduce unnecessary radiation dose to the patient
  - # not to degrade the image quality
- Measurement
  - # Half-life
  - # Individual characteristic radiations emitted by individual radionuclides
    - γ-ray emission radionuclide: multi-channel analyzer (MCA)
    - pure β emission radionuclide: β-spectrometer or liquid scintillation counter



Radionuclidic purity

- multi-channel analyzer




```
**************************************************************************
*****           P E A K   W I T H   N I D   R E P O R T            *****
**************************************************************************

     Detector Name:  DET01
     Sample Title:   FDG
     Peak Analysis Performed on:  2014/2/22  09:58:32 AM
               Peak Analysis From Channel:     35
               Peak Analysis To Channel:     1024
     Tentative NID Library:   C:\GENIE2K\CAMFILES\GMSF18.NLB
     Peak Match Tolerance :   20.000 keV

    Peak  ROI  ROI    Peak     Energy   Net Peak Net Area  Continuum  Tentative
     No. Start End  Centroid    (keV)     Area    Uncert.    Counts    Nuclide

F    1    81-  114   100.51   159.69  3.85E+002   49.55   1.90E+003   .....
F    2   232-  300   267.05   500.30  6.78E+003   93.32   1.17E+003   F-18
F    3   510-  558   532.89  1043.97  4.34E+002   28.51   2.70E+002   .....
```

Radionuclidic purity

- Impurities arise from
  - # the radionuclides produced by various nuclear reactions in a target as well as the impurities in the target material.
  - # Fission of heavy elements in the reactor
  - # Mother radionuclide
  - # Example

    ^{123}I: produced by ^{124}Te(p, 2n)^{123}I reaction; $^{124/126/130}$I may be generated.

    ^{99}Mo/^{99}Tc contamination in ^{99m}Tc elution

    ! 0.15 μCi ^{99}Mo/mCi ^{99m}Tc

Chemical purity

Chemical purity

- Chemical identity and purity address non-radioactive materials in the radiopharmaceutical, including by-products, solvents and other residual components used in the production process.
  - # Impurity example: Al in ^{99m}Tc eluate; Kryptofix 2.2.2 in ^{18}F-FDG; Stavudine in ^{18}F-FLT
- Problems that can occur in the presence of impurities: the human body side effects, pharmacological or toxic effects.
- Determination: gas chromatography, HPLC, spectrophotometry, ion exchange and solvent extractions, etc.

* Additive(additives), Acid, alkali, buffer is not considered an impurity.

Biological test

Biological tests

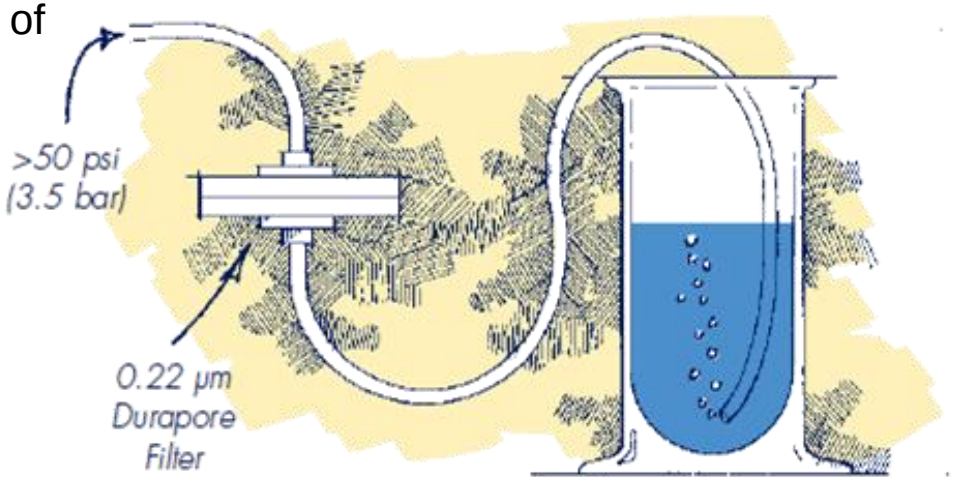
- Sterility
  - absence of any viable bacteria or microorganisms in radiotracers
  - prohibit completion of the sterility testing before the release of finished products, due to the short half-lives of most radionuclide.
- Method of sterilization
  - Autoclaving
    - 121˚C heated to 15-20 minutes.
    - For thermally stable, water-soluble radiopharmaceuticals: $^{99m}TcO_4^-$, ^{111}In-DTPA, ^{111}In-chloride, ^{67}Ga-citrate
  - Membrane filtration
    - 0.22 μm aseptic membrane filter
    - for heat-labile or short-lived radiotracers

Biological tests

- Sterility test
  - US FDA has recommended a 30-hr window for ^{18}F-FDG within which the sterility test must be started
  - tested by incubating the test sample with both Soybean Casein Digest Medium (SCD) at 20~25°C and Fluid Thioglycollate Medium (FTM) at 30-35°C for 14 days.
  - SCD is a culture media for aerobic bacteria and fungi while FTM is a media for anaerobic bacteria.
  - Turbidity in the media would be indicative of the presence of a microbial contaminant.
  - If no evidence of microbial growth is found, the product to be examined complies with the test for sterility.

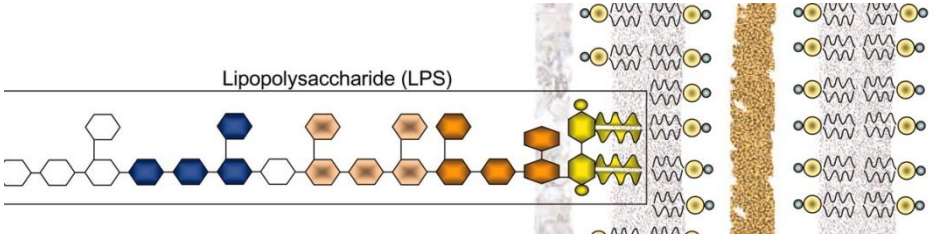
Biological tests

- Bubble-Point Test
  - Filter integrity test of membrane should be done before and after filtration
  - the most commonly used method for the membrane integrity testing
  - A bubble point is the measure of the amount of air pressure required to force an air bubble through a wetted pore.
  - The pressure at which a steady stem of bubbles is noticed is referred to as the bubble point and it should be a standard value (e.g., > 50 psi) for a specific pore-size of a membrane filter.



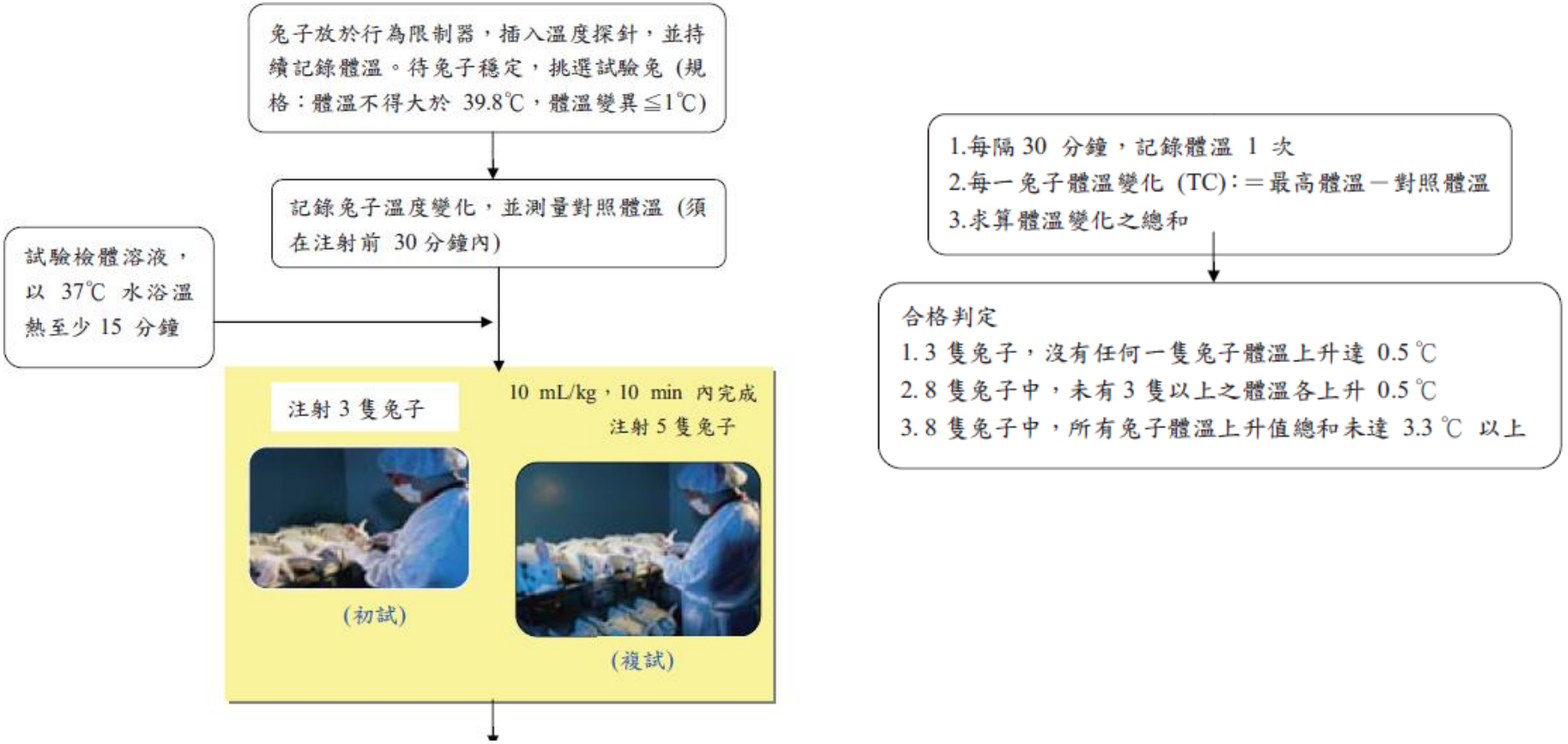
Biological tests

- Pyrogen:
  - a substance that induces fever, e.g. polysaccharides, dead bodies or proteins produced by the metabolism of microorganism.
- Endotoxin
  - lipopolysaccharide complex that forms the outer envelope of gram-negative bacteria
  - The presence of endotoxin in the bloodstream can cause fever, inflammation, and irreversible shock.
  - The radiopharmaceutical limit was set at 175 EU per adult dose for IV or IM injection.
  - heat stable to 250˚C



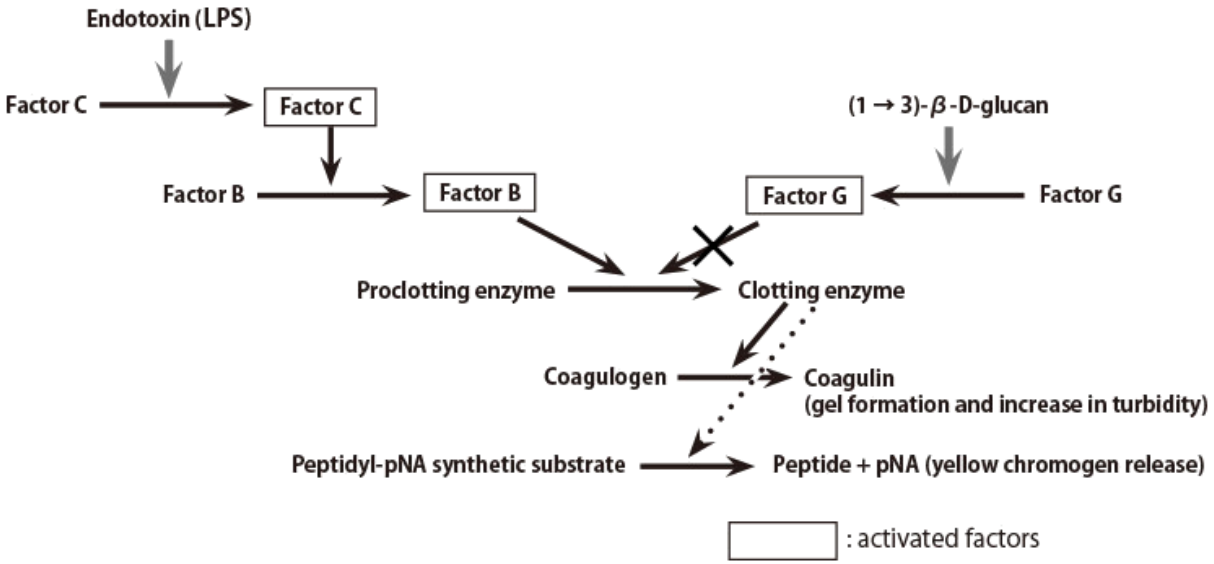
Biological tests

- Bacterial Endotoxin Test
  - # USP Rabbit Test



Biological tests

- Bacterial Endotoxin Test
  - # Limulus Amebocyte Lysate (LAL) Endotoxin Test
    - *Limulus* Amebocyte Lysate (LAL) : an aqueous extract of blood cells of horseshoe crab (鱟)



http://www.wako-chem.co.jp/lal/en/lal_knowledge/about_lal_measurement.html

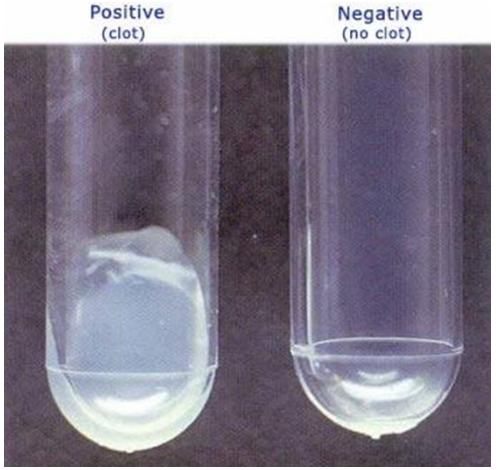
Biological tests

- Bacterial Endotoxin Test
  - # Limulus Amebocyte Lysate (LAL) Endotoxin Test
    - Mix 0.1 ml of LAL and test sample at pH 6 to 8.
    - The reaction takes place within 15 to 60 min after mixing and depends on the concentration of endotoxin
    - three basic LAL test methodologies:

      (1) The gel-clot method

      (2) The chromogenic method } Photomeric method

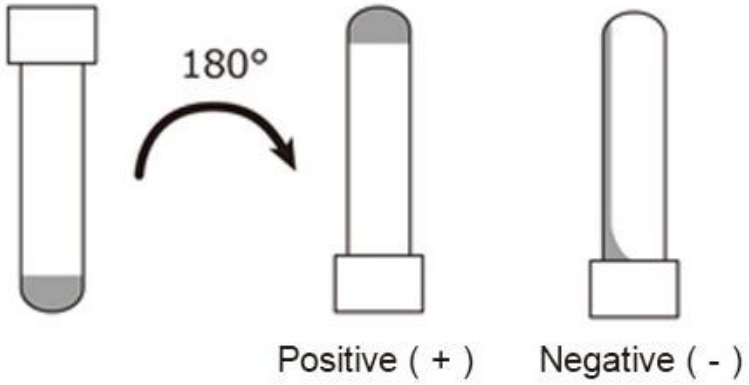
      (3) The turbidimetric method

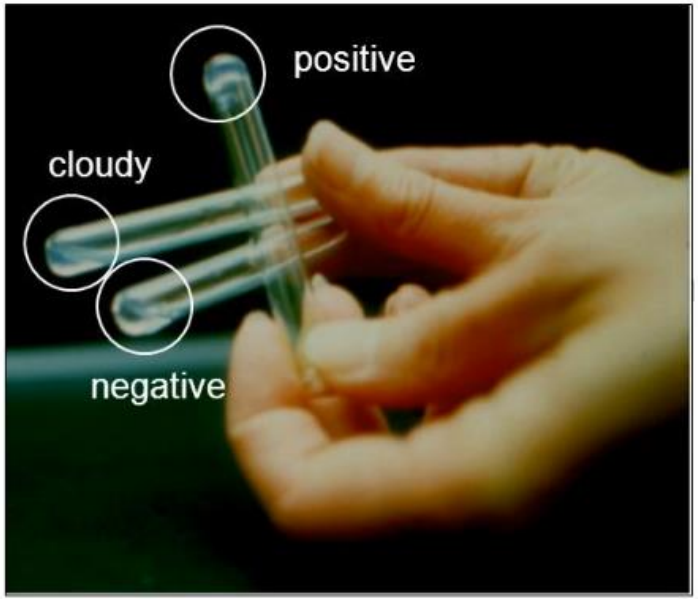


The gel-clot method

Biological tests

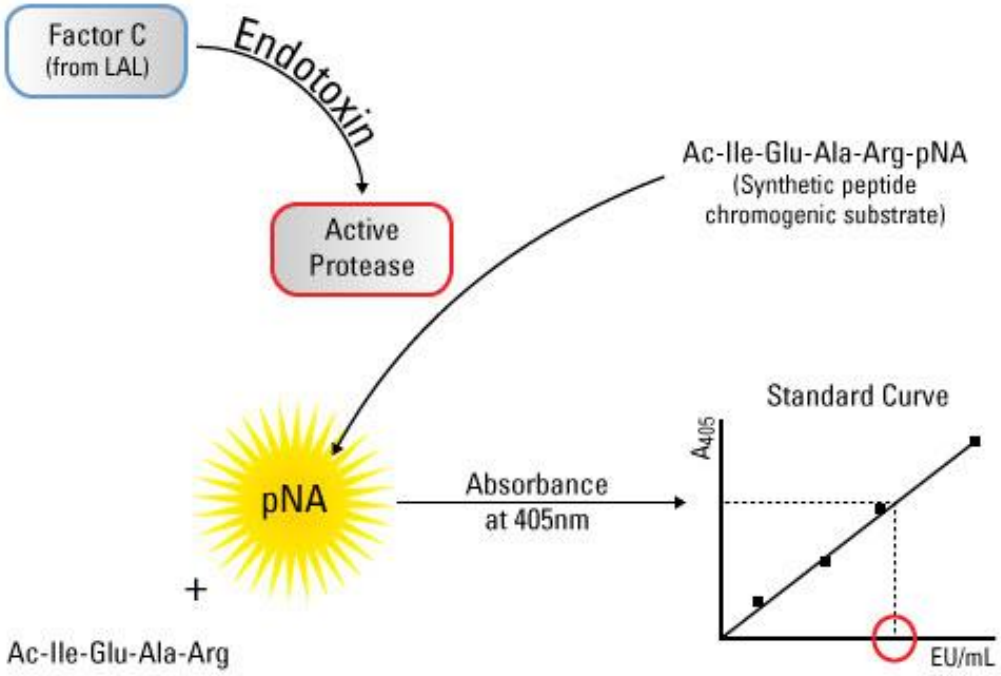
- Gel-clot technique





Biological tests

- Chromogenic Endotoxin Quantitation



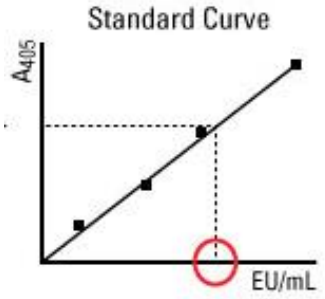
LAL Chromogenic Endotoxin Quantitation reaction scheme. A small volume of the sample is combined with the LAL, and endotoxins in the sample activate the proteolytic activity of Factor C. When the chromogenic substrate is added, the activated protease catalyzes the cleavage of p-nitroalinine (pNA), resulting in yellow color that can be quantitated by measuring the absorbance at 405nm and extrapolating against a standard curve.

Biological tests

- Chromogenic Endotoxin Quantitation

Endotoxin Std

WFI FDG 0.05 0.5 5 PPC

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Thank you….

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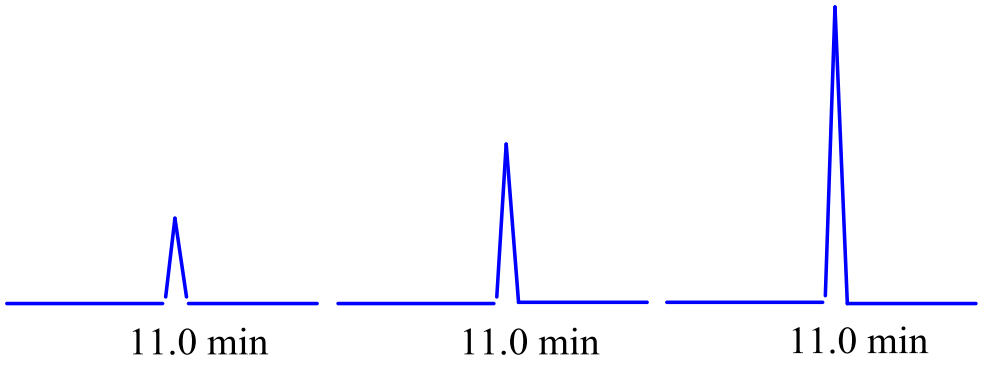
Specific activity (SA)

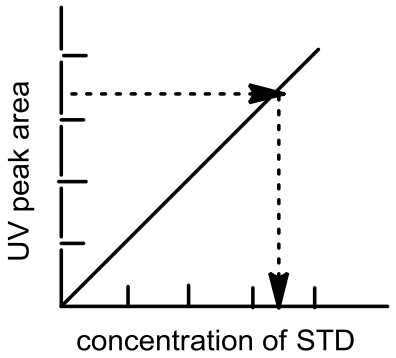
HPLC method

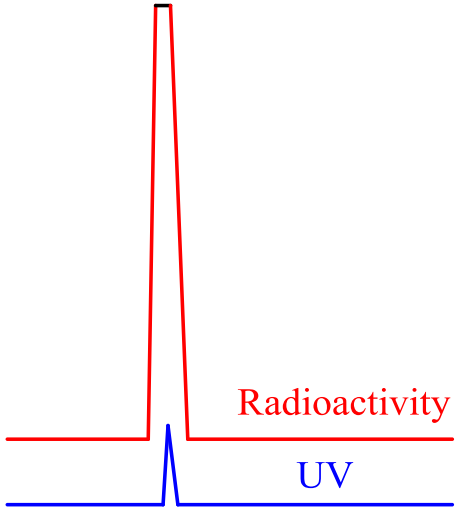
Standard: UV detector



HPLC analysis of cold standards (different concentration)

Standard curve





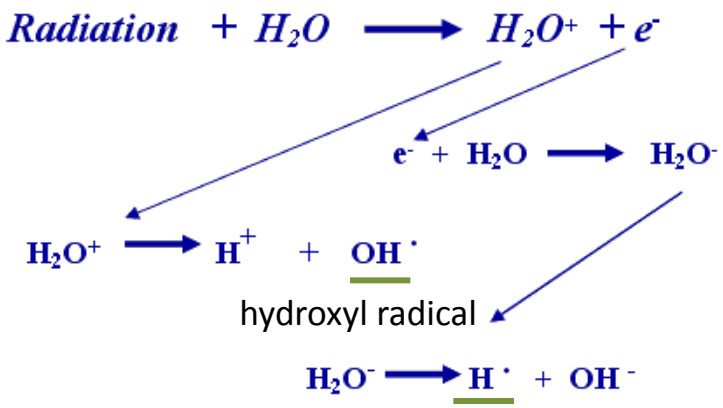
1) Inject pure radiotracer, record time and radioactivity injected

2) Measure UV area of radiotracer, calculate the amount of radiotracer injected according to the standard curve

3) Calculate the specific activity:

Specific activity = radioactivity/amount of radiotracer (time decay corrected to the end of synthesis time)

Radiation degradation (radiolysis)



1. Two hydroxyl radical can combine to form hydrogen peroxide (H_2O_2) that is converted back to water by the organelle called the peroxisome:

$$OH^\cdot + OH^\cdot \rightarrow H_2O_2$$

Hydrogen peroxide

2. The hydrogen radical and the hydroxyl radical can combine to form water:

$$H^\cdot + OH^\cdot \rightarrow H_2O$$

3. The hydrogen ion and hydroxyl ion can combine to form water:

$$H^+ + OH^- \rightarrow H_2O$$

4. The hydrogen free radical can combine with molecular oxygen to form a highly reactive hydroperoxyl radical which continues the chain of radical damage to biomolecules:

$$H^\cdot + O_2 \rightarrow HO_2^\cdot$$

Hydroperoxyl radical

https://www.ceessentials.net/article3.html

Quality control of ^{99m}Tc-radiotracers By ITLC

	Solid Phase / Mobile Phase	Rf Radio-pharmaceutical	Rf Impurity
Pertechnetat	ITLC-SG/0.9% NaCl	Front	Start
^{99m}Tc-DMSA	ITLC-SG/ 2- Butanone	Start	Front
^{99m}Tc-Diphosphonates MDP, DPD, HEDP	A) ITLC-SG/ 1M NaAcetate B) ITLC-SG/ 2-Butanone	Front Start	Start Front
^{99m}Tc-DTPA	A) ITLC-SG / NaCl B) ITLC-SG / 2-Butanone	Front Start	Start Front
^{99m}Tc-ECD	Ethylacetate / Baker Silica gel	Front	Start
^{99m}Tc-HMPAO	A) ITLC-SG/ 2-Butanone B) ITLC-SG/ 0.9% NaCl	Front Start	Start Front
^{99m}Tc-IDA-Derivates	A) saturated saline solution / ITLC-SG B) 50% Acetonitril / ITLC-SG	Start Front	Front Start
^{99m}Tc-Colloids	ITLC-SG / 2-Butanone	Start	Front
^{99m}Tc-MAA	ITLC-SG / 2-Butanone	Start	Front