



# PRACTICAL CONSIDERATIONS

## DIFFERENCES BETWEEN LABORATORY AND LARGER SCALE PROCESSES



# DIFFERENCES BETWEEN ACADEMIC AND PROCESS CHEMISTRIES

**Academic** – Discovers, reveals, disputes, confirms, brings new knowledge.

Small amount of material.

**Process** – Selects, optimizes, seeks for efficiency, defines control points, considers efficiency and environment (also safety).

Role of chemical engineers.

Relatively large amount of material.

# BASIC CONSIDERATIONS

**Laboratory (medicinal) chemistry** (mg – g) has to be **diverse** and **flexible**; chromatography is very common;  
Can be done by a synthetic chemist only;

**Process (up-scaled) pathway** (kg – 1000 kg) must provide **reliable** results, the procedure is expected to be **robust**, **repeatable**, **simple**, **economic**, focuses on **safety** (both operators and patients); chromatography is to be avoided;  
Must be done in mutual cooperation of a synthetic chemist (**thinks in steps**) and a chemical engineer (**thinks in unit operations**)



# BASIC CONSIDERATIONS

## What is scale-up?

Transferring a lab-scale chemical process to pilot or commercial equipment with:

- same yield
- same selectivity
- same quality

Scale-up is **NOT** a simple linear increase in geometric dimensions






# BASIC CONSIDERATIONS

**What is scale-up?**

MORE

- understanding of critical parameters
  - how to control them
  - ability to predict performance at any scale
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# BASIC CONSIDERATIONS

*Laird, T. – How to Minimise Scale Up Difficulties*


1. Appropriate conditions
2. Correct dosing time
3. Hazards
4. Mass transfer issues
5. Solvent extractions
6. Optimising using statistical methods

Laird, T. *Chemical Industry Digest*, p. 51, July 2010



## **BASIC CONSIDERATIONS**

**The best way to minimize the scale-up problems is by important data gathering and detailed process understanding.**



# DIMENSIONAL ANALYSIS

• **Ideally**, dimensions in geometry, velocities of the components, forces on the system, temperatures and concentrations should be kept constant between different scales

- **Surface area per volume ratio** (serious consequences for heat removal and heat input during process scale-up);
- **Kinematic similarity** – they exists when two systems have the same shape and the ratios of the velocities between corresponding places are also equal; Fluid dynamics – the Reynolds number ( $Re$ ) – it increases during scale-up at a constant stirrer speed as the diameter of the stirrer increases;
- **Hydrodynamic similarity** – they exists when the ratios of forces between corresponding places are also equal in both systems;



# DIMENSIONAL ANALYSIS

- **Thermal similarity** – temperature differences between corresponding places in a system have a constant ratio with one another (temperature profile, heat transfer area);
- **Chemical similarity** – concentration differences between corresponding places in two systems have a constant ratio to one another (ratio between the chemical conversion rate, rate of molecular diffusion).

# DIMENSIONAL ANALYSIS

Maintaining geometrical similarities for various scales is not practical in batch processing as the jacket heat-exchange area per unit reduces significantly with a scale

	Reactor Size [L]	Surface Area [m <sup>2</sup> ]	Surface Area / Volume [m <sup>2</sup> /L]	Factor
Lab Scale	0.5	0.02	0.04	28.6
	10	0.20	0.02	14.3
Pilot Plant Scale	380	2.32	0.0061	4.4
Large Production	38 000	53.0	0.0014	1

# DIMENSIONAL ANALYSIS

## Reynolds number

- gives a measure of the degree of turbulence or the ratio of inertial force to viscous force (the higher Reynolds number the higher turbulence of the system)

$$R_e = ND^2 \rho/\mu \text{ (mostly for homogeneous systems)}$$

$R_e$  ... Reynolds number

$N$  ... rotational speed (revolutions per second)

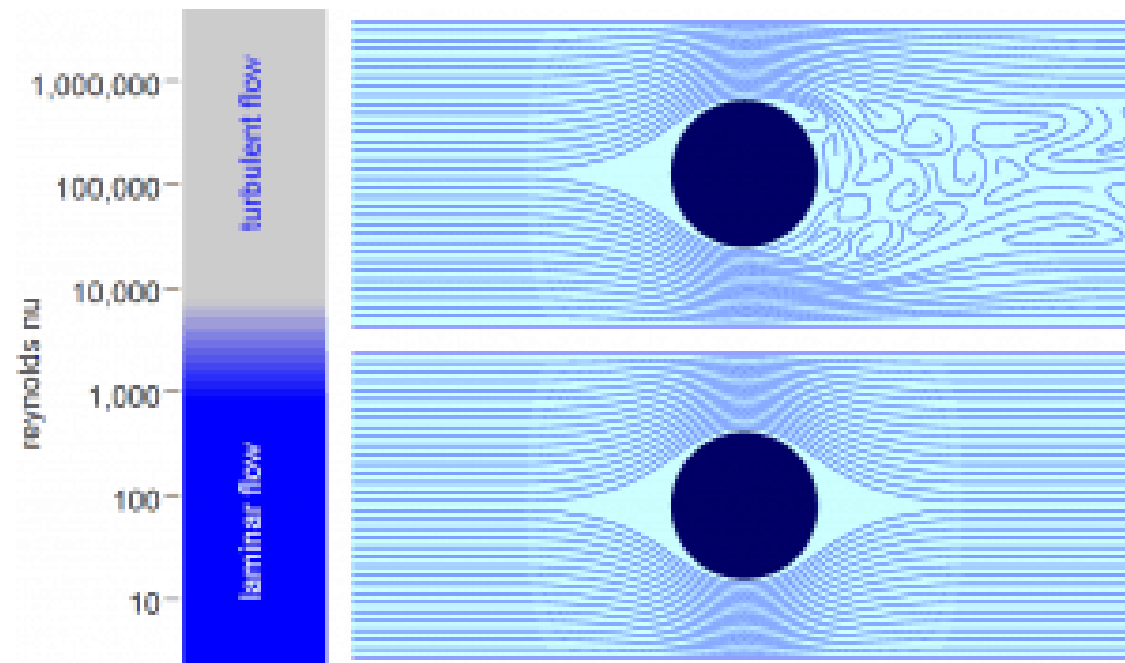
$D$  ... diameter of the stirrer (m)

$\mu/\rho$  ... kinematic viscosity ( $\text{m}^2/\text{s}$ )

# LAMINAR VS. TURBULENT FLOW

- **Laminar flow** – is characterized by smooth or regular paths of fluid particles. The fluid flows in parallel layers with minimal lateral mixing.

**Turbulent flow** – is characterized by irregular movement of particles. Lateral mixing is very high.



# MIXING



paddles blade



dispersing homogenizing blade



propeller



achor blade



gate blade



ribbon blade



screw type



Brumagin type



turbine blade



curved blade paddle



spiral propeller blade



flat blade turbine type

# DIMENSIONAL ANALYSIS

○ Maintaining total similarity of **all** possible scale-up parameters on different scales cannot be established and, in fact, **is almost impossible**;

A reliable batch process scale-up cannot be simulated in generally applicable mathematical models without a clear understanding of all process and reaction mechanisms;

**Regime analysis** – significance/trade-off of particular similarities – can be done in an early stage of process development;

# DIMENSIONAL ANALYSIS


Regime analysis can be done in an early stage of the process development:

- If heat effects are relative small, then the thermal similarity will be easily maintained;
- If reaction rate is slow compared to the mixing time, a turbulent regime is not that relevant anymore;
- For very rapid reactions any limitation in diffusion might be the rate-controlling step and the chemical reaction is a subject to a hydrodynamic regime and the energy input should get priority;
- if in a heterogeneous reaction the particle size and, therefore, the dissolution rate is an important process parameter, the chemical regime might dictate a stirrer rate on large scale where all particles are free from bottom of the reactor;



# DIMENSIONAL ANALYSIS

**Stirrer rate** and **diameter of the stirrer** are important parameters to play with in the early stages of process development and that in any realistic process scale-up the larger scale-reactor will always represent higher tip speed and longer circulating and mixing times than on the smaller scale. For heterogeneous processes this fact might have serious consequences.





# DIMENSIONAL ANALYSIS

Widely used scale-up rule is the **equal power per unit of volume criterion** and has given accurate results in many cases. This rule has been concluded to be the best in almost any scale-up problem.

For non-laminar flow (high Reynolds number), with constant geometry and the same stirrer type

$$P/V = P_0 \times \rho \times N^3 \times D^2 = \text{constant}$$

$P_0$  ... power number of the stirrer

$\rho$  ... density

$N$  ... stirrer speed

$D$  ... diameter of the stirrer

# DIMENSIONAL ANALYSIS

Table represents effects of various scale-up strategies from 1 L to 1000 L

Parameter	Power	P/V	Q/V	Tip Speed	Reynolds number
Equal P	1.0	$10^{-3}$	0.0215	0.215	2.15
Equal P/V	$10^3$	1.0	0.215	2.15	21.5
Equal N	$10^5$	$10^2$	1.0	10	$10^2$
Equal Tip Speed	$10^2$	0.1	0.1	1.0	10
Equal Reynolds number	0.1	$10^{-4}$	$10^{-2}$	0.1	1.0

Q/V ... the liquid pumping capacity of the stirrer per volume

# BASIC CONSIDERATIONS

## Why is scale-up so difficult?


- There are no standard approaches for doing quantitative process scale-up;
- Textbooks on scale-up are limited;
- Scale-up practice largely depends upon individual experience;
- There is a shortage of people with the right experience;
- The success of process scale-up depends to a great extent on the communication and transfer of information between the chemists and the chemical engineers;
- There are no systematic ways for a chemical engineer to ask a chemist what information is required for process scale-up and *vice versa*;
- Companies and chemical engineering community are not learning from the success and failures that are occurring on a daily basis throughout the industry;
- There is a gap between how chemical engineers and chemists want the process to run in the plant and how the operators actually run it, due to lack of training or involvement.



# BASIC CONSIDERATIONS

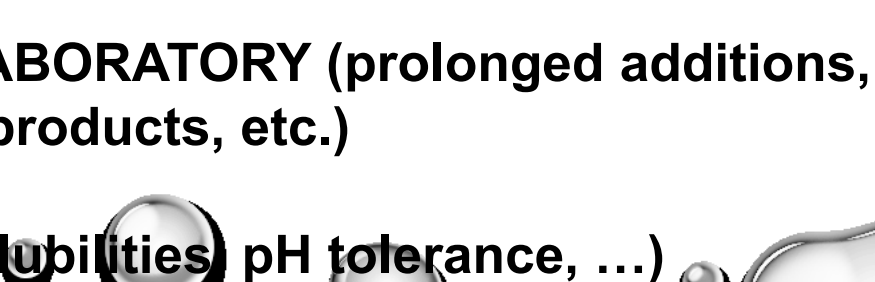


**Process development** should be defined as the process of converting a synthetic route into an optimum, robust, safe and economic process for manufacturing the chemical of desired quality at the desired ultimate scale within a reasonably desired period of time;



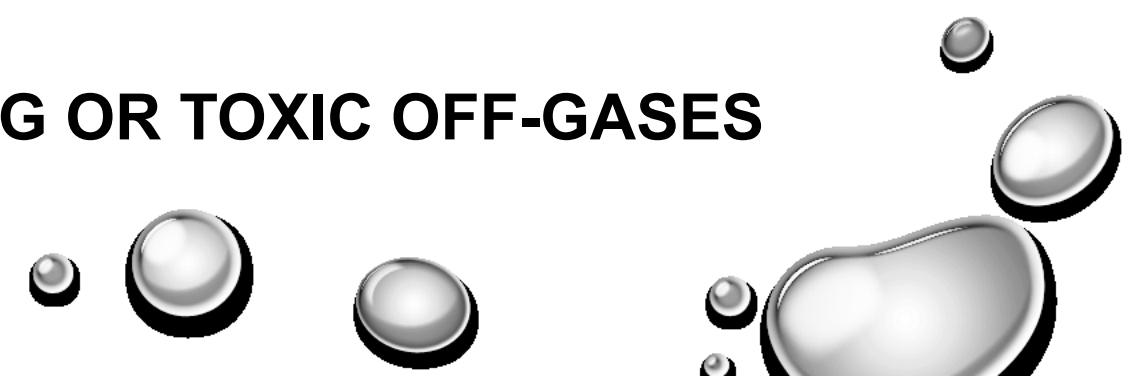


# BASIC CONSIDERATIONS

- **SAFETY**
  - **TEMPERATURE CONTROL**
  - **TEMPERATURE RANGE**
  - **MOBILE (TRANSFERABLE) STREAMS**
  - **INCREASE EFFECTIVITY (MINIMIZE SOLVENTS, INCREASE CONCENTRATION WHERE POSSIBLE)**
  - **STABILITY OF COMPONENTS DURING REACTION AND HOLD ONS**
  - **SIMULATE LARGE SCALE CONDITIONS IN LABORATORY (prolonged additions, heat accumulation, stability of reactants and products, etc.)**
  - **GET INFORMATION ABOUT PROPERTIES (solubilities) pH tolerance, ...)**
- 



# **BASIC CONSIDERATIONS**

- **DETERMINE CONTROL POINTS (in process controls)**
  - **KEEP IT SIMPLE**
  - **ANTICIPATE FATE OF VOLATILE REAGENTS**
  - **DEVELOP EFFICIENT AND STRAIGHTFORWARD WORK UP PROCEDURE**
  - **CONSIDER INERT ATMOSPHERE TO AVOID THE PRESENCE OF MOISTURE AND OXYGEN**
  - **ASSUME SCRUBBING FOR ANNOYING OR TOXIC OFF-GASES**
  - **SUGGEST RESISTANT MATERIAL**
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# CHARGING

- Weighing of reagents (differential, reactors mounted on a load cell);
- Charging of liquids (by weight or by volume) – use the same approach in the laboratory – density of liquids will change slightly with temperature;
- Recommended accuracy (tolerance) - volumes  $\pm 5\%$ , weights  $\pm 2\%$ ;
- Different transfer times considering a laboratory scale and the production (large) scale;

# SOLVENT CONSIDERATIONS

Watch out hydrocarbon solvents with even number of carbons (toxicity, electrostatic buildup);

Classification of solvents – **ICH Harmonised Guideline Q3C** – Impurities: Guideline for Residual Solvents

**Class 1** – solvents to be avoided (known human carcinogens, strongly suspected human carcinogens, and/or environmental hazards, e.g. carbon tetrachloride (concentration limit 4 ppm), 1,2-dichloroethane (5 ppm), 1,1,1-trichloroethane (1500 ppm), benzene (2 ppm))

**Class 2** – solvents to be limited (non-genotoxic animal carcinogens, agents of irreversible toxicity, e.g. acetonitrile (410 ppm), chlorobenzene (360 ppm), chloroform (60 ppm), *N,N*-dimethylformamide (880 ppm), hexane (290 ppm), methanol (3000 ppm), *N*-methylpyrrolidone (530 ppm), toluene (890 ppm))

**Class 3** – solvents with low toxic potential (permissible daily exposure 50 mg or more per day, e.g. acetic acid, acetone, ethyl acetate, heptane, 2-propanol, triethylamine)

Solvents for which no adequate toxicological data was found – a manufacturer is asked to supply justification for residual levels of these solvents (e.g. diisopropyl ether, petroleum ether, trifluoroacetic acid)



# WORK UP

## IN PROCESS CONTROLS (IPCs)

- Off-line analysis

- In-line analysis

- On-line analysis

## WORK UP

Efficiency – e.g. crystallization directly from the reaction mixture;

- labor cost is very important;

Extractions are generally preferred over filtration to remove impurities;

Column chromatography is rare and very expensive;

# WORK UP

- Includes operations after the reaction was declared complete;
- Such operations include quenching the reaction both to remove impurities and facilitate product isolation and to allow **safe** handling of process streams, even after product isolation.
  
- Quenching reactive species
- pH adjustment
- Filtration
- Precipitation
- Extractions
- Concentration (including azeotropic distillation)
- (Chromatography)



## **WORK UP**

Typical time and money saving technique

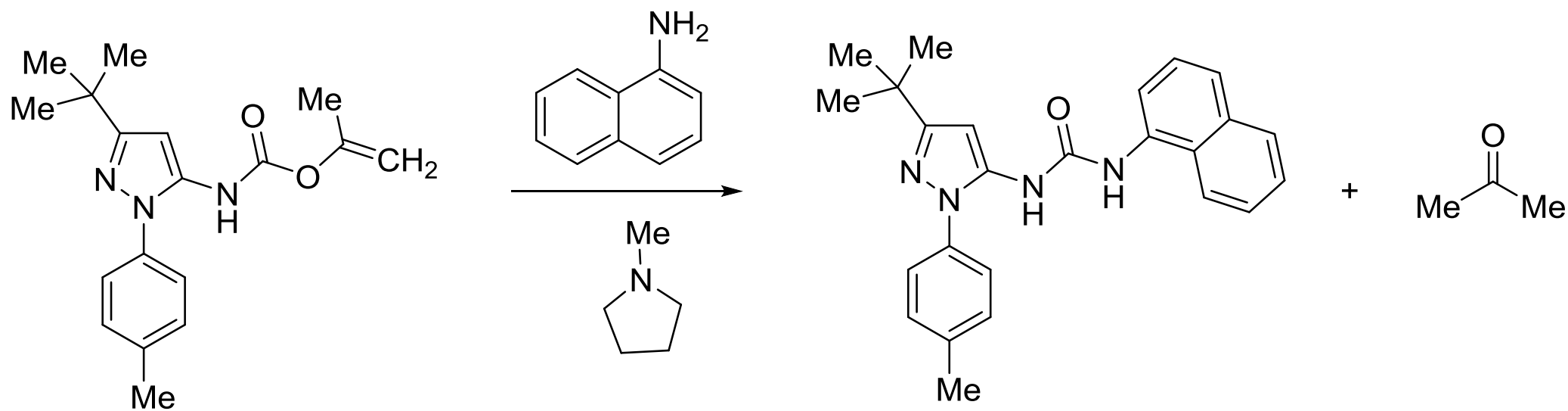
## **TELESCOPING**

The reaction proceeds further without full isolation of an intermediate, with advantage even without any quench;

Pushing a reaction to completion – removal of side products



# WORK UP

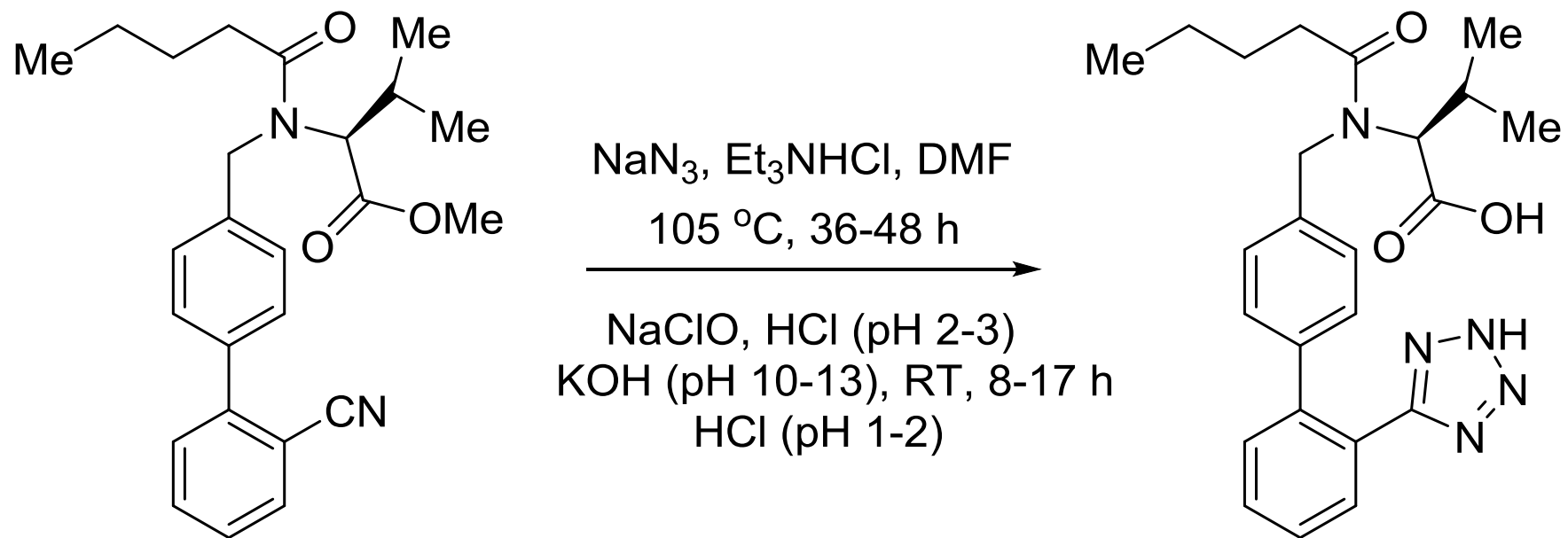


Gallou, F. *et al J. Org. Chem.* 70, 6960 (2005)

# WORK UP

## QUENCHING REACTIONS

Safe decomposition of excessive reagents stops a reaction



Valsartan

## WORK UP

### QUENCHING REACTIONS



### VERY CAREFUL


**Recent issue with the formation of nitrosamines (e.g. limit in Valsartan (320 mg dose) will be 0.03 ppm in 2021**

Careful with halogenated solvents (e.g. dichloromethane) in the presence of azides (diazidomethane !!)



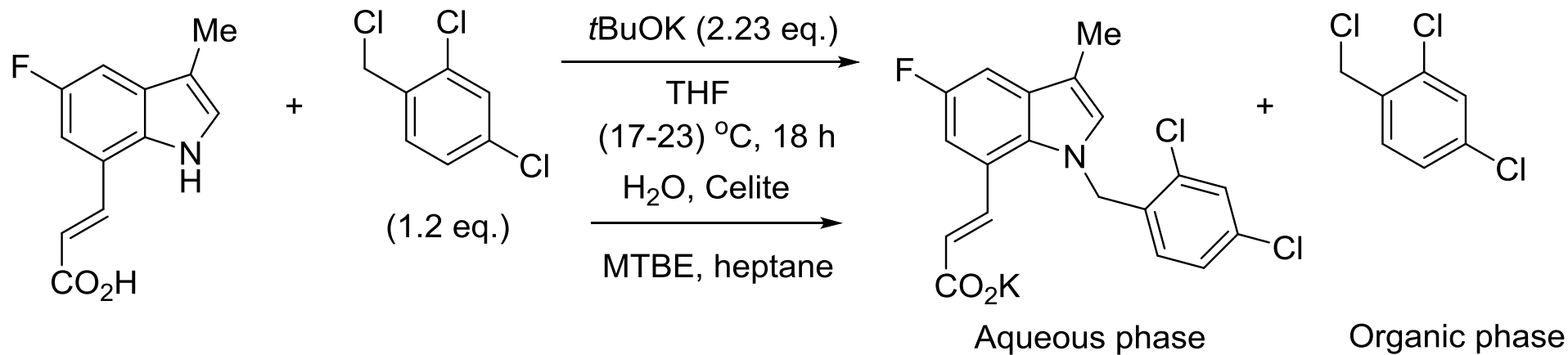
# WORK UP

## EXTRACTIONS

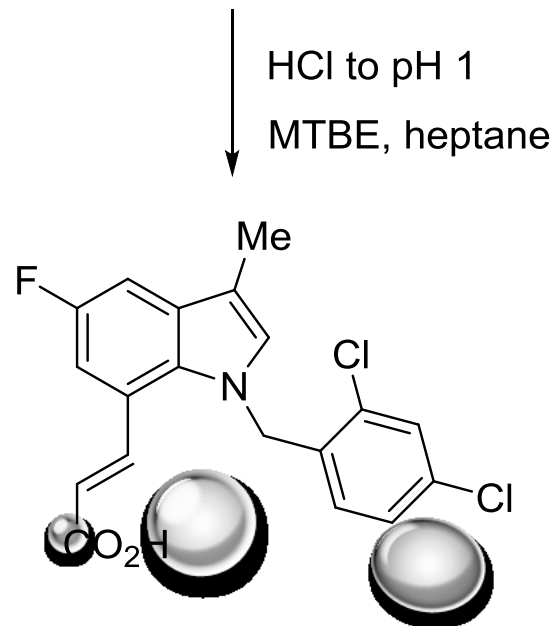
- Used to separate neutral compounds from water soluble components;
  - Solid Phase Extraction (SPE) – separate compounds of significant different polarity;
  - Solubility or miscibility of organic solvents with water;
  - Separation of layers
  - pH value adjustment – extra opportunities;
  - Ionic strength;
  - Solubility at higher temperatures;
- 

# WORK UP

## EXTRACTIONS



Zegar, S. *et al* *Org. Process Res. Dev.* 11, 747 (2007)





# WORK UP

## EXTRACTIONS

### Convenient Aqueous Solutions for Extractions

Solvent	pH of 0.1 N solution	Relative Solubility in Organic Solvents	Comments
HCl	1.1	High	Corrosive, volatile
H <sub>2</sub> SO <sub>4</sub>	1.2	Low	
AcOH	2.9	High	Weak acid
Na <sub>2</sub> HPO <sub>4</sub>	8.5	Low	
NaHCO <sub>3</sub>	8.4	Low	
NH <sub>3</sub>	11.1	Moderate	Volatile
Na <sub>2</sub> CO <sub>3</sub>	11.6	Low	
Na <sub>3</sub> PO <sub>4</sub>	12.0	Low	



# WORK UP

## FILTRATION

**Polish Filtration** – an operation to remove trace amounts of insoluble impurities before other operations – passing a process stream through in-line filters with different porosity;

Very important for crystallizations, avoiding emulsions;

**Ultrafiltration** – protein separation through membranes;





# WORK UP

## PERVAPORATION




**Pervaporation** through membranes – specific for some solvents – a processing method for the separation of the mixtures of liquids by partial vaporization through a nonporous or porous membranes;

Separation of components is based on a difference on a transport rate of individual components through the membrane;

Pervaporation is effective for solutions containing traces or minor amounts of the component to be removed;

**Hydrophilic membranes** for dehydration of alcohols containing small amount of water, **hydrophobic membranes** for removal of traces of organic compounds from aqueous solutions;





## WORK UP


### PERVAPORATION

**Hydrophilic membranes** – commercially most successful membranes are formed from polyvinyl alcohol or polyimides;

**Hydrophobic membranes** – based on polydimethylsiloxane

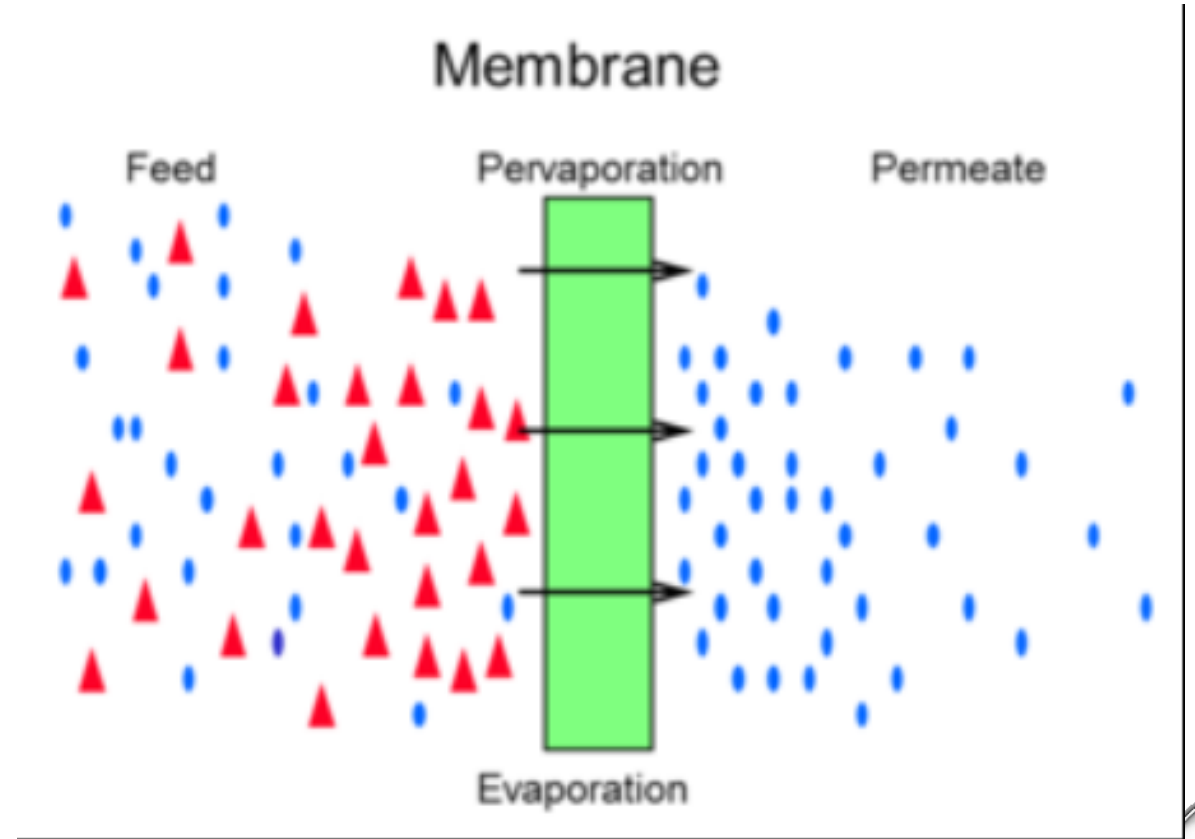
### PRINCIPAL

The pressure difference on sides of a membrane (usually atmospheric vs. vacuum), **permeate** goes through a membrane, **retentate** does not go through and thus it is separated.



# WORK UP

## PERVAPORATION



# WORK UP

## CHROMATOGRAPHY

Best to avoid, technically difficult and expensive on large-scale, but still used in special cases (preparative chromatography);


Solid Phase Extraction

Simulated Moving Bed Chromatography

<https://www.youtube.com/watch?v=Harx2khTuEc>



## EFFICIENT PROCESS DEVELOPMENT

- **Anticipate and avoid problems**
  - **Do experiments at minimum and maximum ranges to confirm robustness/sensitivity in cases where a particular parameter is significant**
  - **Identify critical impurities within the whole process and their fate**
  - **Get maximum allowed level of critical impurities**
  - **How to proceed if the specification criteria in IPCs are not met?**
  - **Pay attention to details, observe unusual changes**
  - **Avoid systematic errors**
  - **Take into account future process validation**
- 

# PROCESS VALIDATION

- The cumulative effort to demonstrate reliable processing and product quality;
- The fruition of the labor of process chemists and engineers, the ultimate tests of how well one understands the process;
- Before 1970s little attention has been paid to efficient process development;
- 1987 – FDA – Guideline on General Principles of Process Validation (validation is defined as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes);
- 2008 – FDA – process validation is the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products; the quality is built up into the product through process understanding and cannot be tested in batches – quality by design (QbD)