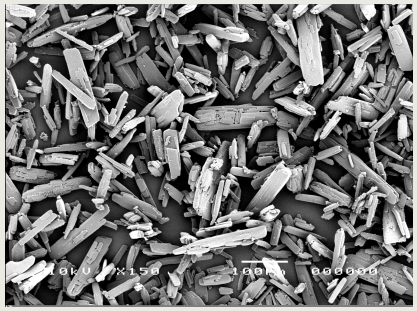
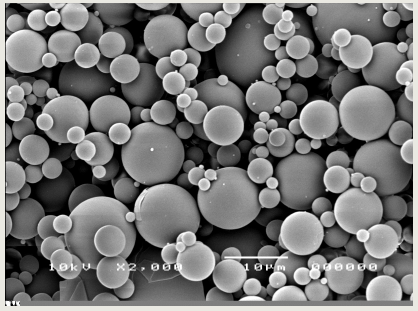
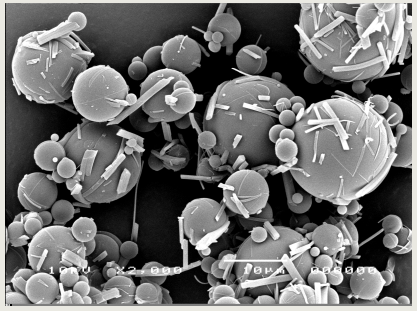
THE DANISH
DANMARKS
UNIVERSITY OF
FARMACEUTISKE
PHARMACEUTICAL
UNIVERSITET
SCIENCES

PHYSICAL STABILITY OF SPRAY DRIED SOLID DISPERSIONS OF AMORPHOUS TOLFENAMIC ACID AND POLYVINYLPYRROLIDONE K-30

Pia Thybo
The Danish University of Pharmaceutical Sciences
Copenhagen, Denmark

Outline of Today's Presentation

Introduction

- Spray drying method
- Amorphous versus crystalline material
- Stabilization - solid dispersions

Specific study

- Tolfenamic acid
- Methods
- Results (stability, dissolution)

Summery

Spray Drying

- Simple up-scaling. Unique ability to produce specific particle size and volatile content regardless of dryer capacity

- Continuous reliable operation. Powder quality remains constant throughout the dryer run time under constant operating conditions

- Ability to handle heat sensitive, thermoplastic and/or hygroscopic materials

Spray Drying - Continued

•Ability to handle solutions, suspensions, emulsions, pastes or melts

• Ability to handle materials under cGMP and aseptic drying conditions

• Ability to handle hazardous substances i.e. flammable solvents, dust explosion hazards, toxic materials

• Wide choice of spray dryer designs allows product specifications to be met by tailoring the design

Examples of Spray-Dryers

Laboratory scale

Pilot scale

Production scale

Applications in the Pharmaceutical Industry

Formation of micro-particles

Inhalable products

- Particle size
- Particle size distribution

Micro encapsulation

- Controlled Release formulations
- Masking of a bad taste

Polymorphism

- Solubility/dissolution

Key Elements in Spray Drying

Atomization

of liquid feed into a spray of droplets

Droplet-Gas Contact

mixing and flow pattern

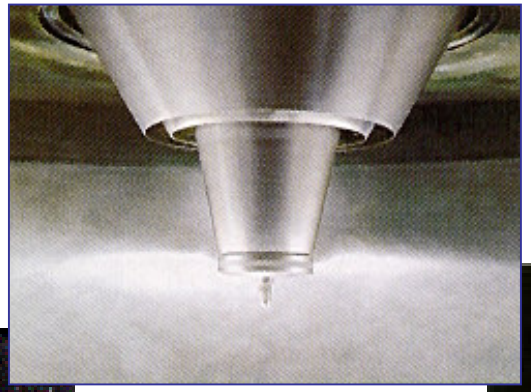
Drying of Droplets

moisture / volatiles evaporation (~ 10 sec.)

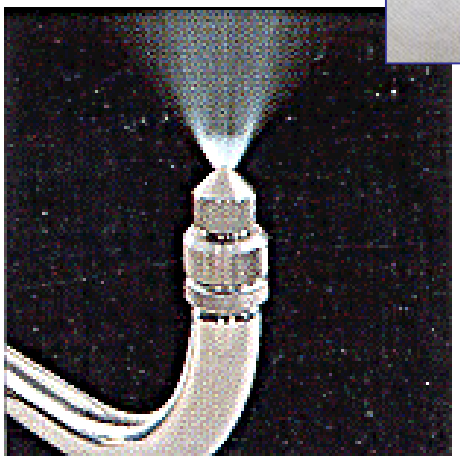
Product Recovery

separation of particles from the gas

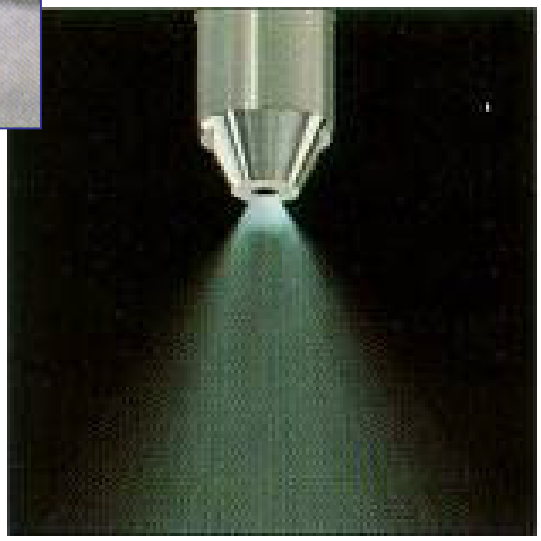
Atomization



Rotary atomizer



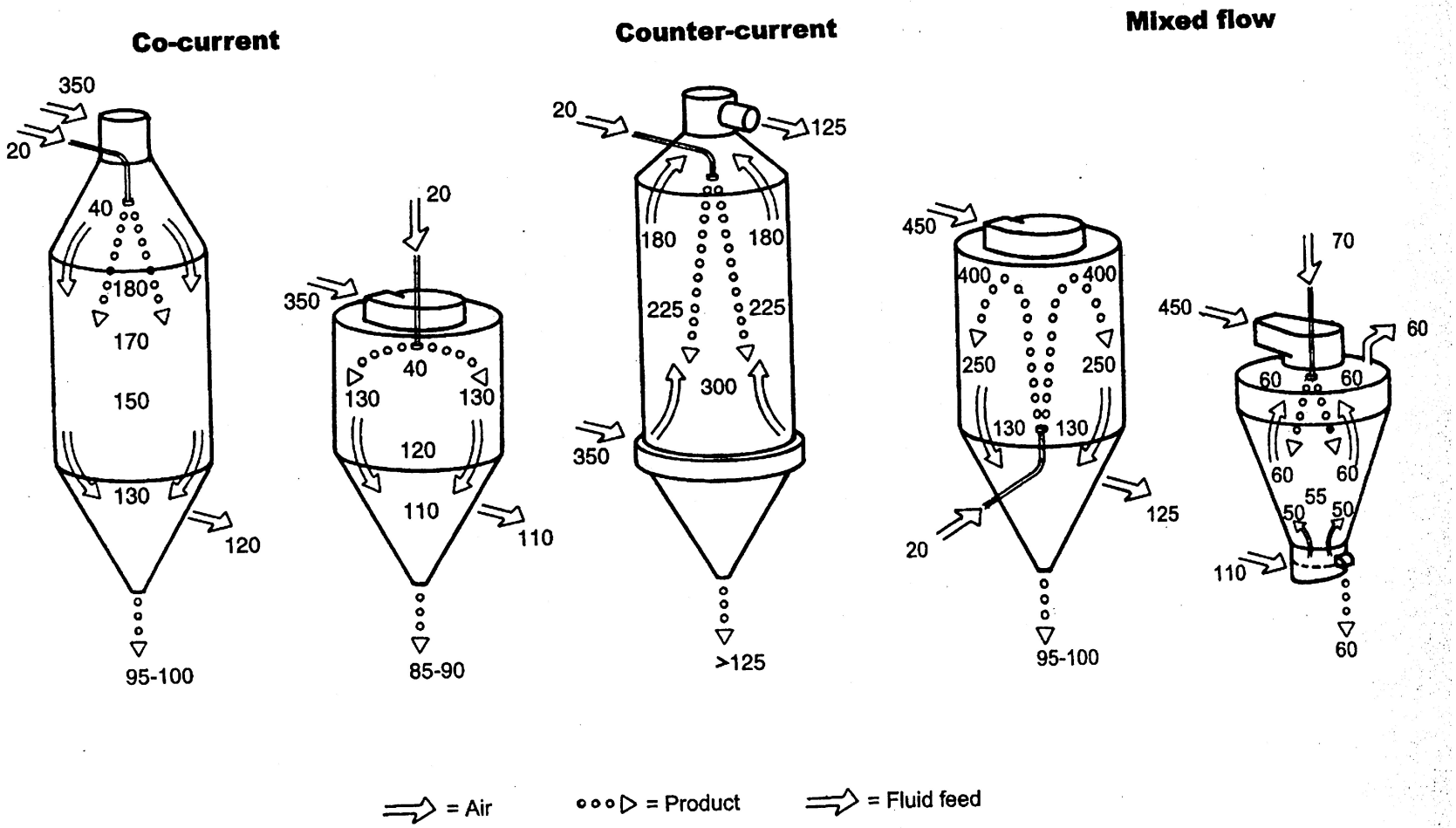
Two-fluid nozzle
fountain mode



Two-fluid nozzle
Co-current mode

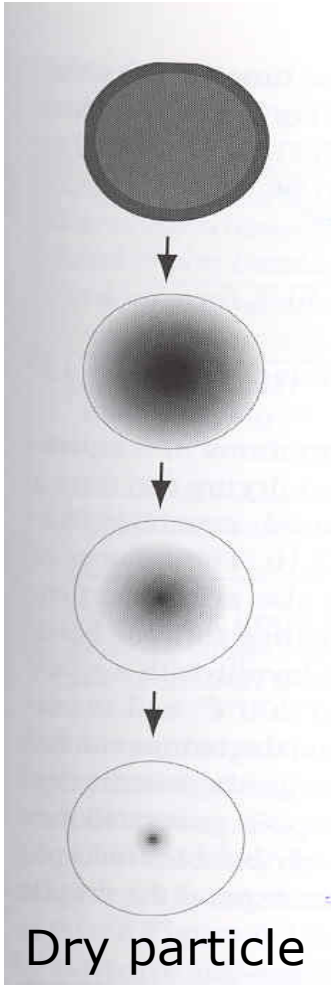
Pressure nozzle

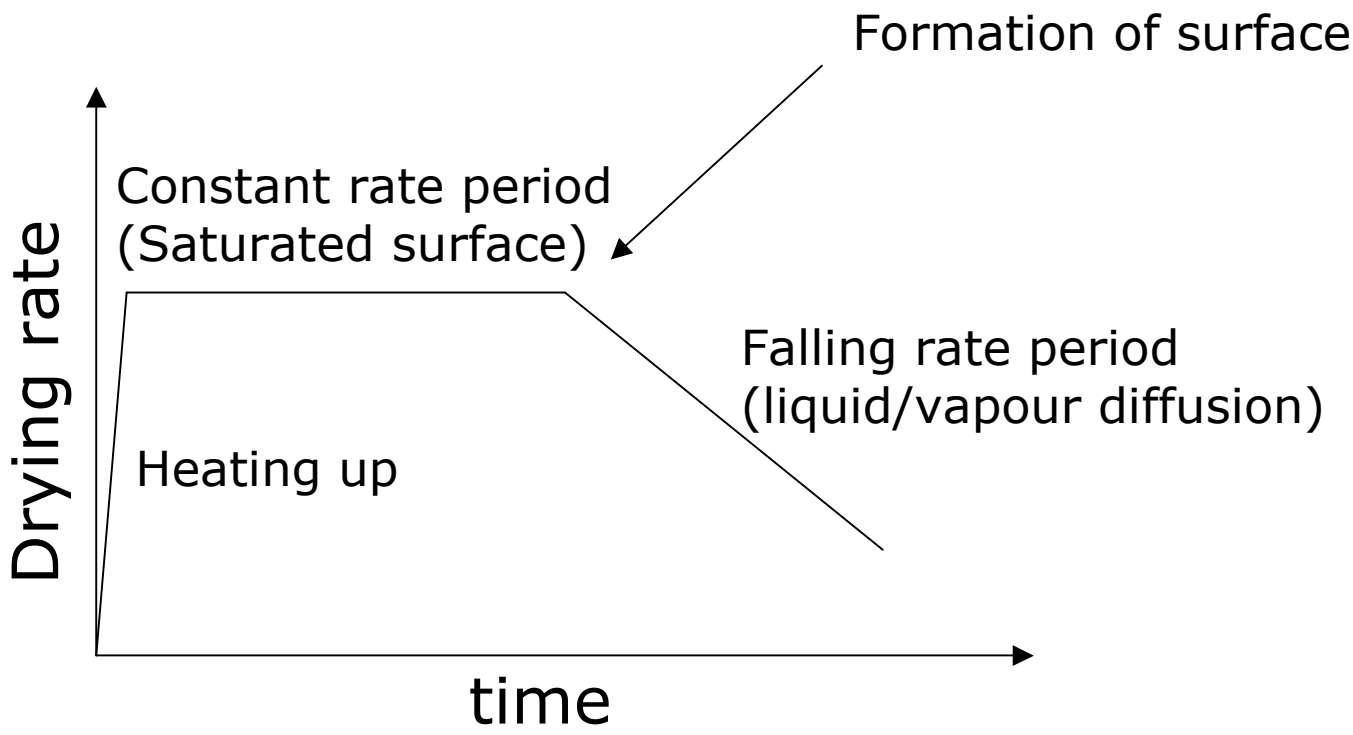
Droplet-Gas Contact



Ref.: Masters 2002

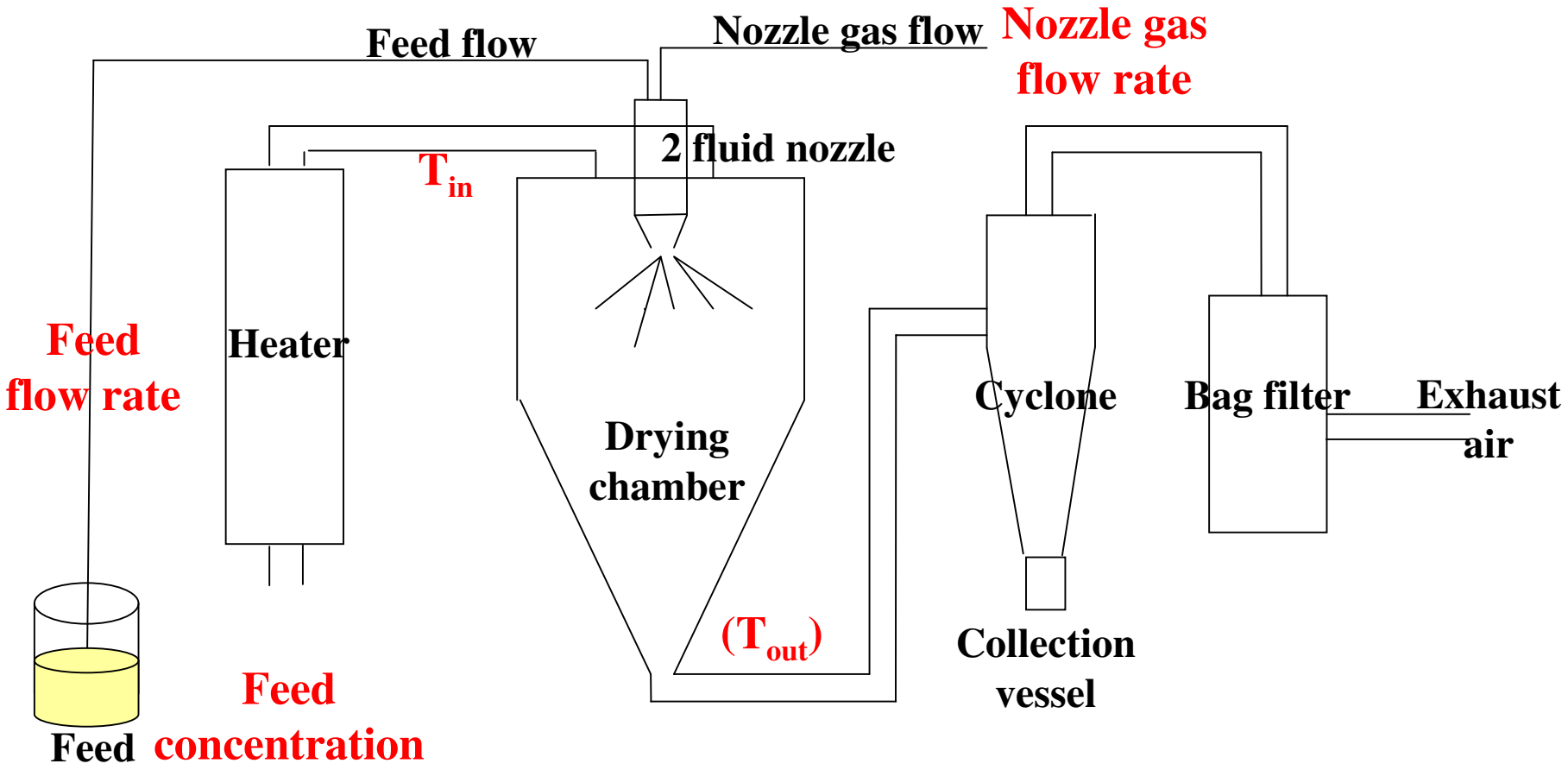
Drying – From Droplet to Particle





Ref.: Masters 2002

Schematic picture of spray drying process



Effect of Spray Drying Parameters

Particle size

Feed concentration, Atomization ratio (Atom. gas flow rate/Feed flow rate), Outlet temperature, Particle morphology, Nozzle type

Volatile content

Outlet temperature, Drying gas flow rate (residence time), Particle morphology, Particle size

Particle morphology

Solvent and carrier choice, Outlet temperature, Formulation

Yield

Particle size, Volatile content, Particle Morphology

Amorphous versus Crystalline - Definition

Crystalline

…"the adjective, *crystalline*, implies an ideal crystal in which the structural units, termed *unit cells*, are repeated regularly and indefinitely in three dimensions in space"

Vippagunta et al, Advanced Drug Delivery Reviews, 48, 2001

Amorphous

"Similar to a crystalline solid an amorphous solid may have short-range molecular order, but unlike a crystalline solid, an amorphous solid have no long-range order of molecular packing"

L. Yu., Advanced Drug Delivery Reviews, 48, 2001

Amorphous versus Crystalline

Positive

- Improved dissolution rate
- Bioavailability

Negative

- Stability
- More hygroscopic

Physical Stability

• The glass transition temperature (Tg) is often used to predict stability

• As a rule of thumb Hancock et al. (1995) proposed that the Tg of a pharmaceutical product should be at least 50 ºC above the storage temperature

• Stabilization approaches are often necessary for amorphous pharmaceutical drugs

Physical Stability – Moisture sorption

- Absorbed water act as plasticizer, increasing molecular mobility resulting in a reduced Tg
- Absorbed water can alter the hydrogen bonding between molecules

→ Phase separation often accompanied with re-crystallization

Stabilization - Solid Dispersions

Several studies have shown the potential of high Tg polymers to inhibit/retard re-crystallization of amorphous drugs

Mechanisms

- Anti-plasticizing effect
- Interactions between drug and polymer
- Enchanged solubility

Specific Study

Purpose

To increase the dissolution rate of Tolfenamic acid through manipulation of solid state properties

The intension is to produce small amorphous particles prepared by spray drying method

Stabilization of this high-energy amorphous form by addition of crystal growth inhibiting compounds

The Drug – Tolfenamic Acid

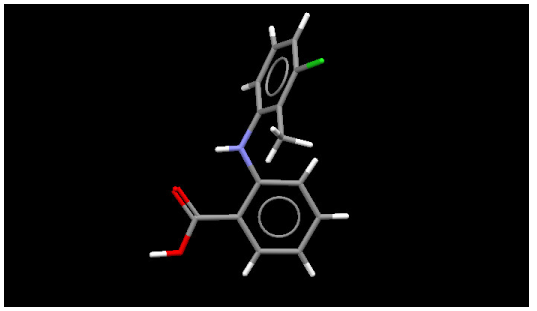
- NSAID

- White and yellow polymorph
(conformational – geometry of amino group)
Hydrogen bonded dimers in crystal

- Comparable solubility
Solubility in water: ~ 50 µg/ml
Solubility in ethanol: ~10 mg/ml

- Solutions of both modifications are colourless and have identical physical properties

Yellow polymorph



White polymorph

Preliminary Experiments

Part 1: Composition of feed solution

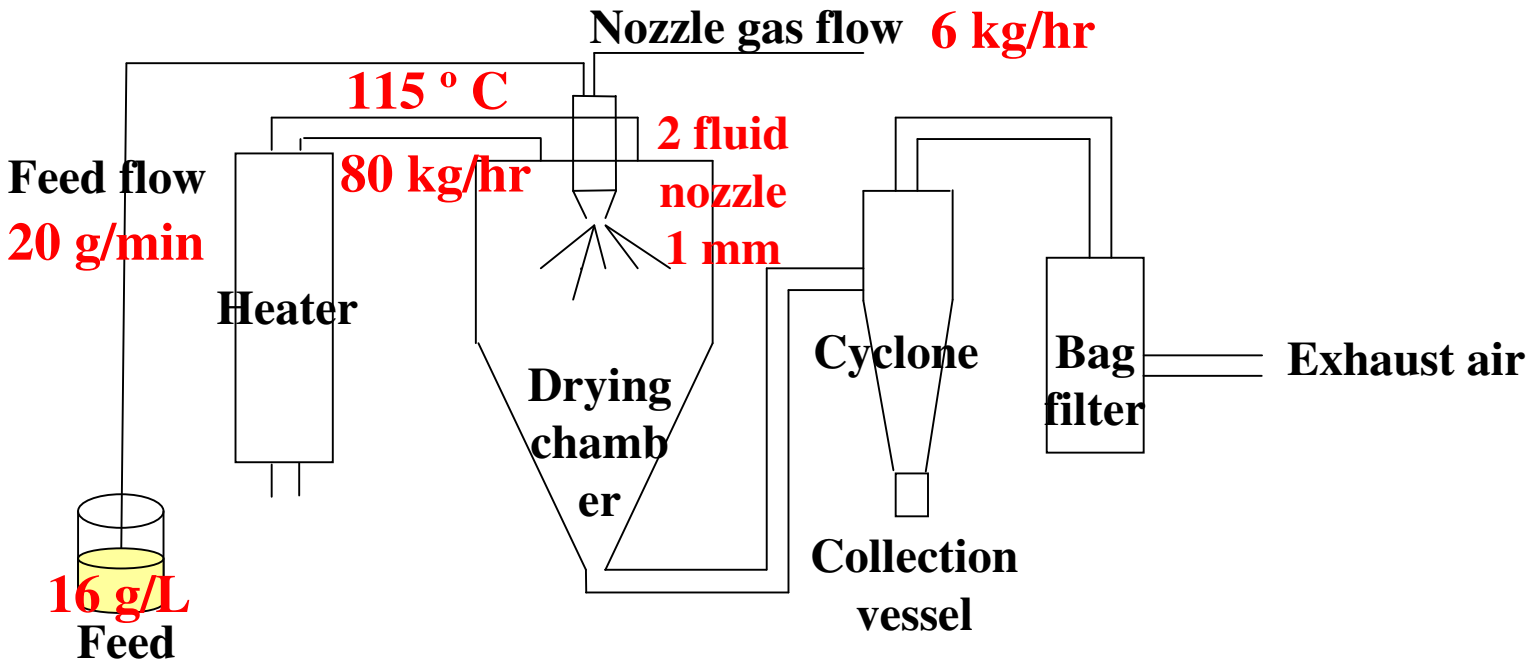
- Screening of suitable excipients, primarily within the water soluble polymers
- Selection of drug/polymer ratios
- Selection of solvent for feed solution
- Concentration

Choices:

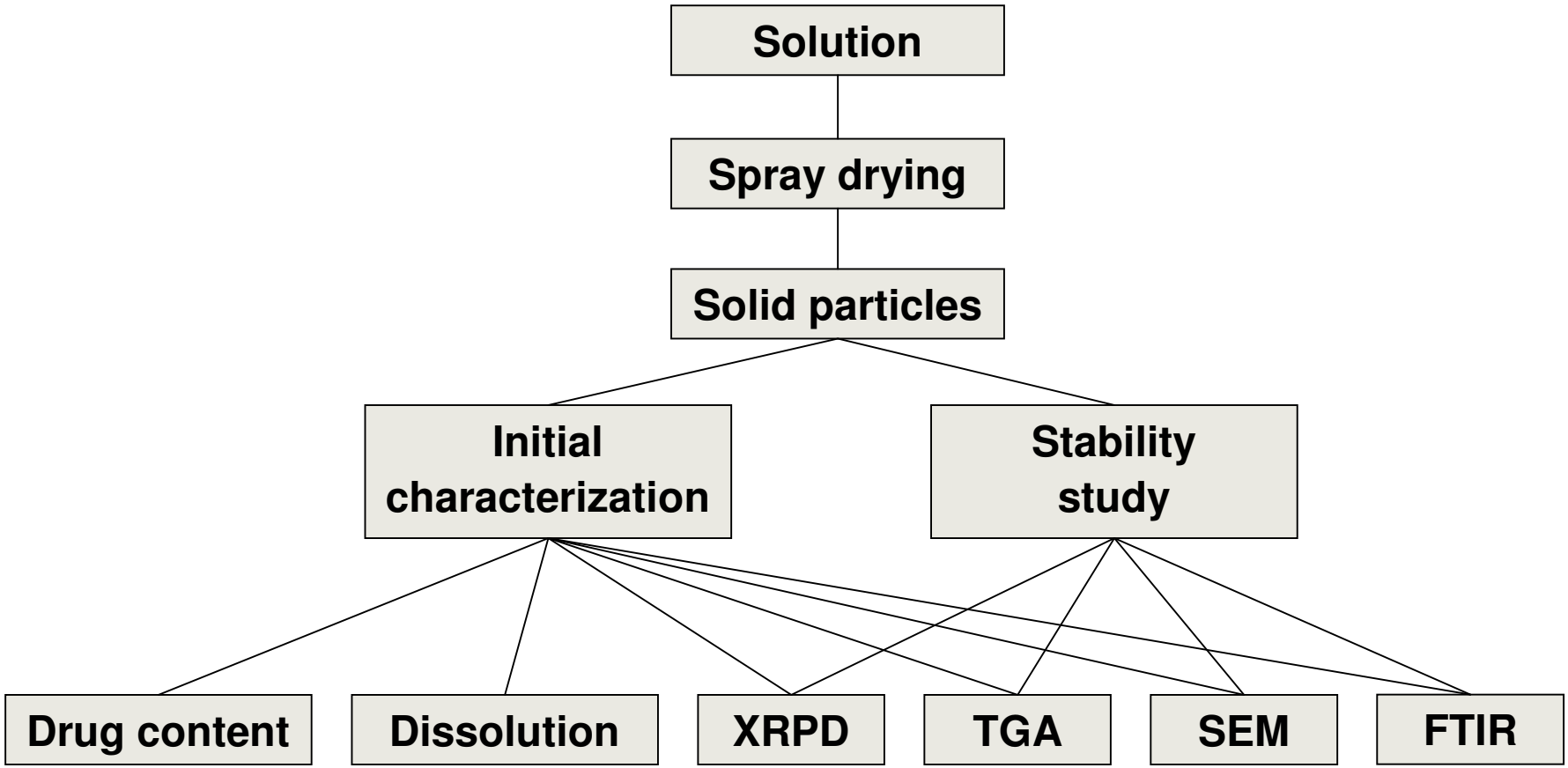
- Formulation as solid dispersion with PVP as excipient
- Drug/polymer ratio: (1:1, 1:3, 1:5, 1:7)
- Ethanol as solvent

Preliminary Experiments

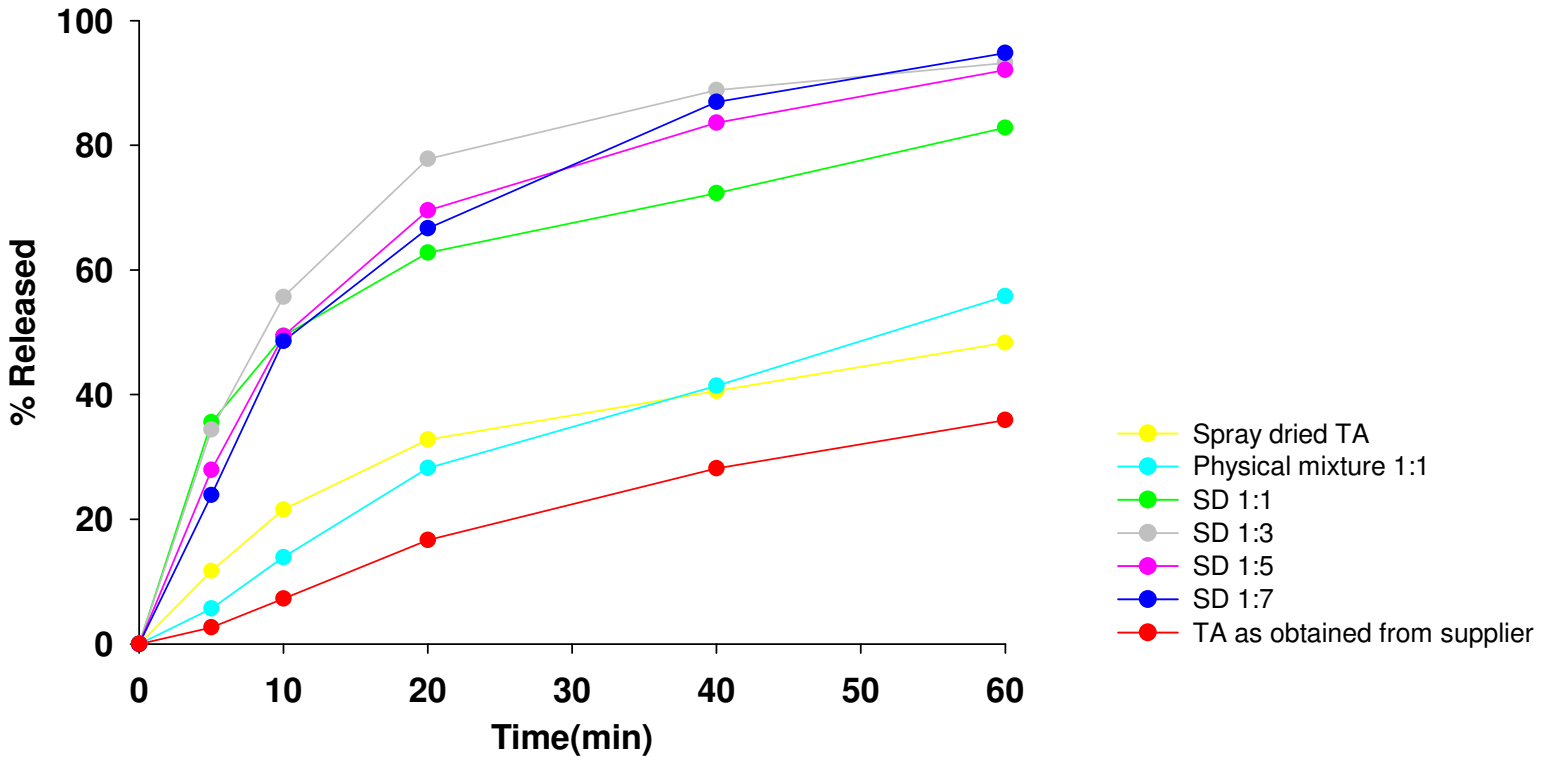
Part 2: Optimization of the spray drying process (process parameters)



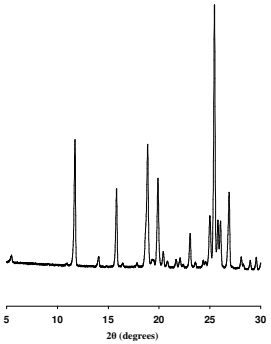
Preparation & Characterization

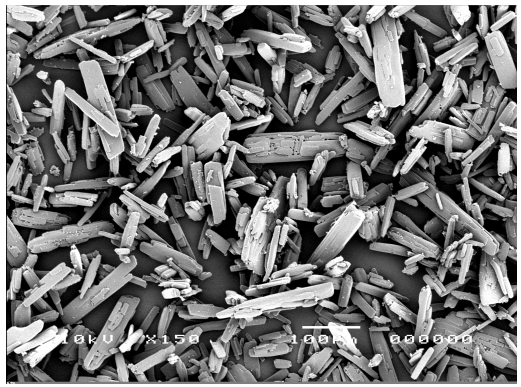


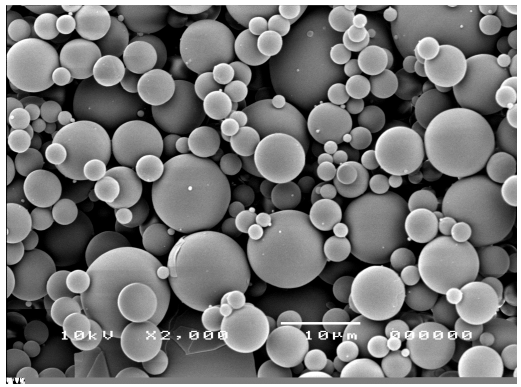
Dissolution

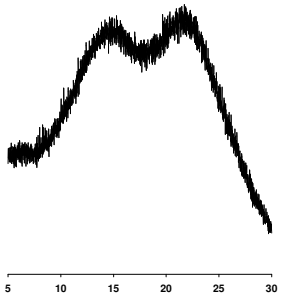


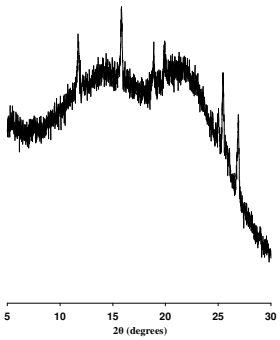
Morphology, Crystallinity & Stabilization

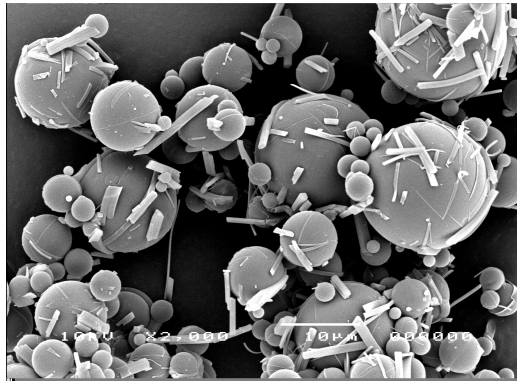


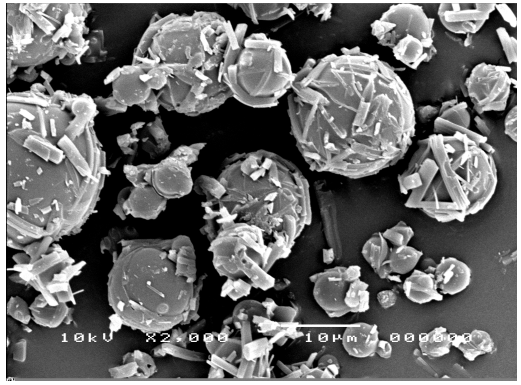


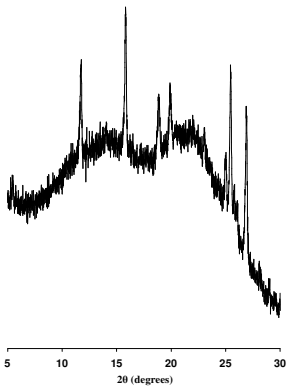






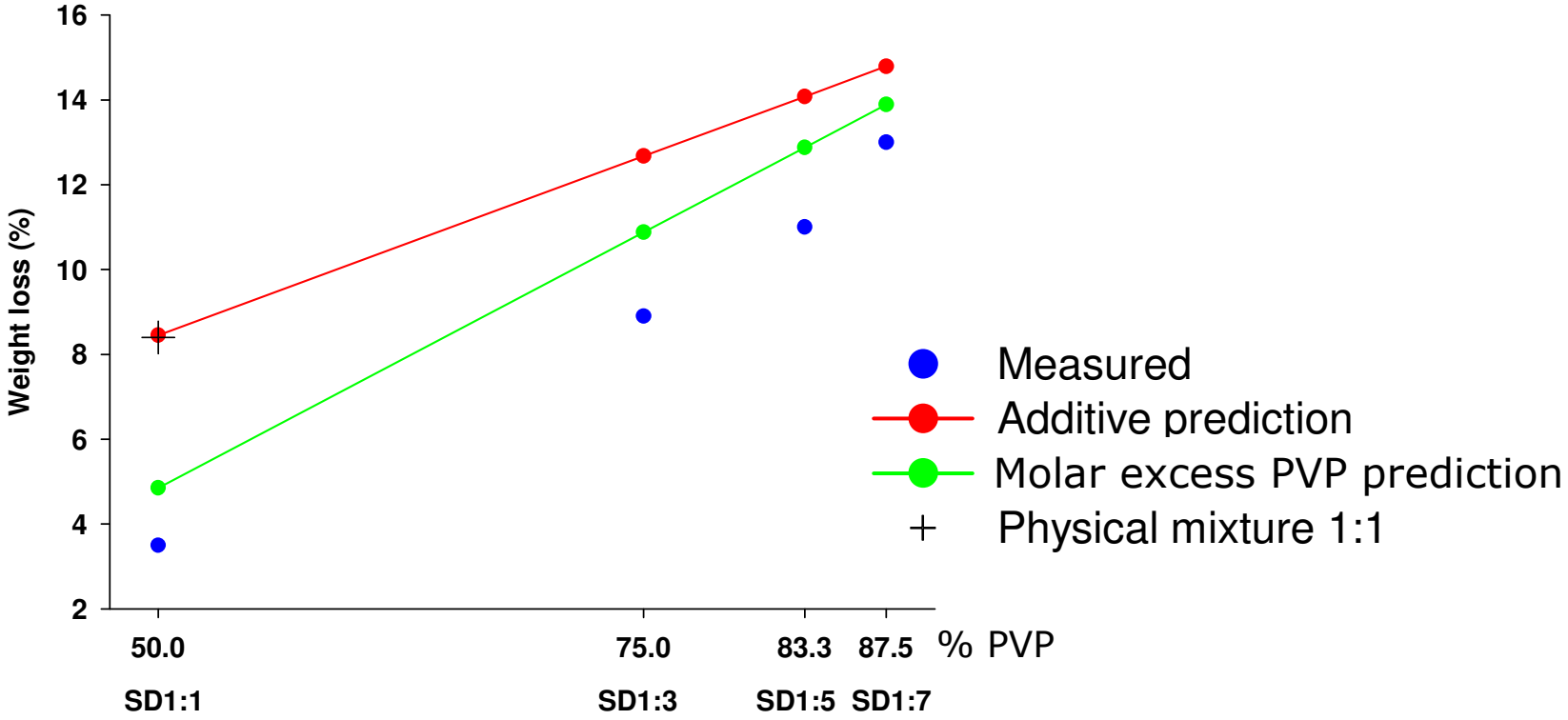






SD 1:1 12 weeks SD 1:1 24 weeks

Stability - Interaction



Measured after 12 weeks storage – equilibrium reached

Main Conclusions from Study - Summery

- Able to transform tolfenamic acid into its amorphous form in solid dispersions
- All solid dispersions show higher dissolution rate when compared to physical mixture and starting material
- The drug to polymer ratio is important from a stability point of view
- Indication of intermolecular interaction in the solid dispersions

More Interested……..

The presented data is included in a paper accepted for publication in Pharmaceutical Development and Technology (January 2007).

Acknowledgments

- Lars Hovgaard, DUPS (main supervisor)
- Flemming Hansen, University of Copenhagen (XRPD)
- Sandoz (financial support)
- Drug Research Academy (financial support)