Az SZTE Kutatóegyetemi Kiválósági Központ tudásbázisának kiszélesítése és hosszú távú szakmai fenntarthatóságának megalapozása a kiváló tudományos utánpótlás biztosításával”

ÚJ SZÉCHENYI TERV

Gyógyszertudományok Doktori Iskola
Ph.D. kurzus (GYTKDIE16)

„Introduction to melt extrusion and application of quality by design principles”

2012. 03. 27. – 03. 30.

„Solid dispersions: Types, production, characterization”

Prof. Dr. Peter Kleinebudde

TÁMOP-4.2.2/B-10/1-2010-0012 projekt

MAGYARORSZÁG MEGÚJUL

A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

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UNIVERSITÄT DÜSSELDORF

Introduction to melt extrusion and application of quality by design principles

Szeged, March 26-30, 2012

Peter Kleinebudde
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PSSRC Pharmaceutical Solid State Research Cluster

Content

- Solid dispersions: Types, production, characterization
- Introduction to melt extrusion: Equipment, process, materials, properties of extrudates, downstream processing, applications
- PAT applications for melt extrusion and multivariate analysis of spectral data
- Tools for risk analysis in the context of melt extrusion
- Approaches to develop a design and a control space

Solid dispersions

- Definition
- Types
- Properties
- Applications
- Production
- Characterization

Solid dispersions: Definition

- "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method" *(Chiou and Riegelman 1971)*
- "a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles" *(Dhirendra et al. 2009)*

Solid dispersions: Types

Term	Solid Solution	Glassy Solid Solution	Compound Complex Formation	Solid Crystal Suspension	Eutectic Mixture	Amorphous Precipitation	Glassy Suspension
Phases	1	1	1	2	2	2	2
Drug	molecularly dispersed	molecularly dispersed	molecularly dispersed	crystalline	crystalline	amorphous	amorphous crystalline
Carrier	crystalline	amorphous	crystalline amorphous	crystalline	crystalline	crystalline	amorphous

- One or more phases
- Drug is dispersed molecularly, as amorphous particles or crystalline particles
- Carrier is crystalline or amorphous
- Drug and carrier are miscible in molten state or not

Ostwald-Mier diagram

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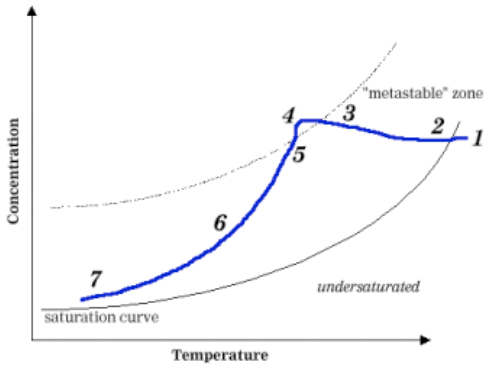
- Solubility curve
- Thermodynamic equilibrium
- Kinetic stabilisation
- Supersaturation
- Crystallisaton
  - Nucleation
    - spontaneous
    - induced
  - Crystal growth



1 Feed location, undersaturated
2 Solution cools to saturation
3 Enter "metastable" zone, nucleation begins
4 Rapid nucleation
5 Concentration decreases with crystal growth
6 Crystal growth during main cooling cycle
7 Exit location, supersaturated

Ostwald Mier diagram

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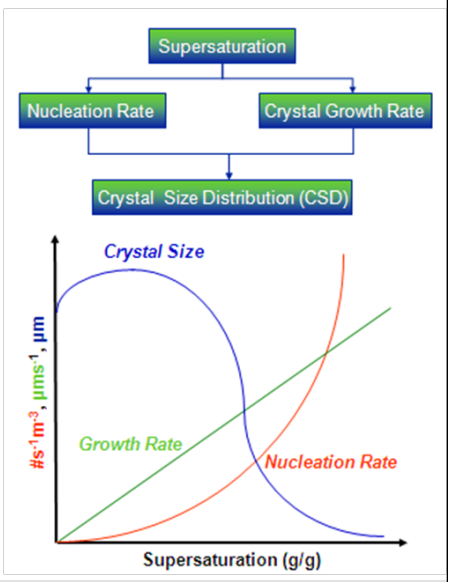
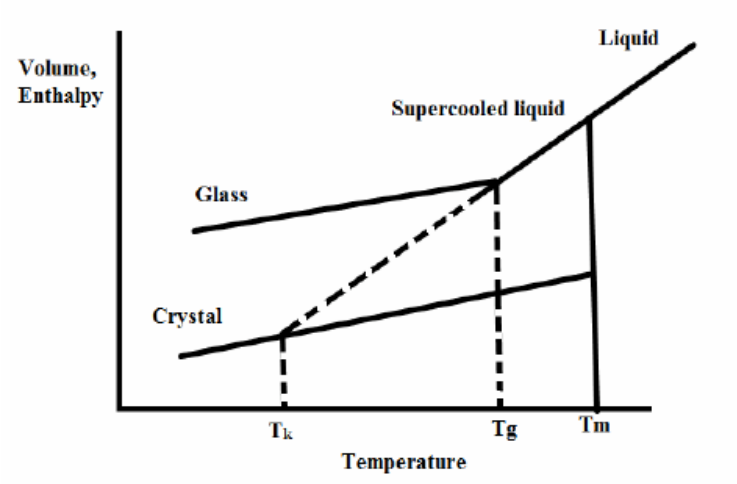
- Cooling, drying, addition of antisolvent etc.:
- slow
  - Large particles
  - Higher crystallinity index
- Fast
  - Small particles
  - Lower crystallinity index
- Ultra fast
  - Amorphous systems



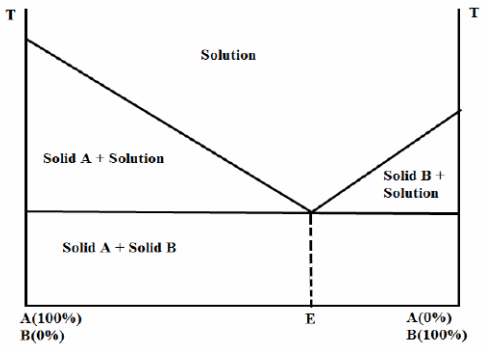
Solid dispersions: Properties



Glass transition temperature T_g

- Mobility of chain segments increases above T_g
- Hardness, elasticity, viscosity, swelling, hydrolysis, diffusion coefficient etc. change drastically at T_g
- Plasticizer can decrease T_g
  - Internal plasticiser: change of the polymer structure by introduction of large substituents or branching
  - External plasticiser: low molecular liquids with low vapour pressure and high affinity to the polymer
  - Cave: water (T_g of 135K) is a plasticizer for many hydrophilic polymers

Solid dispersions: Types



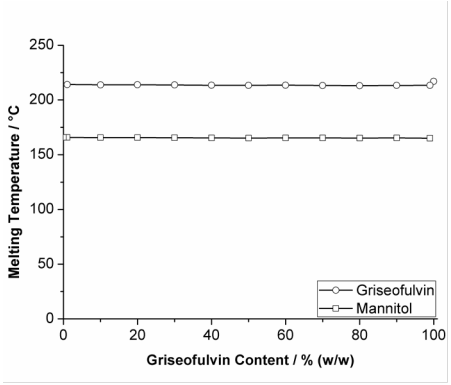
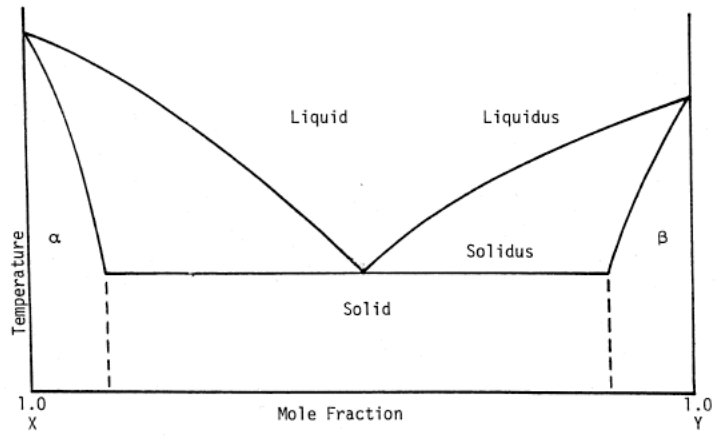


Figure: Phase Diagram of Griseofulvin and Mannitol determined by DSC (-25 to 250°C, 10K/min, n =3)

Eutectic mixture

Solid crystal suspension

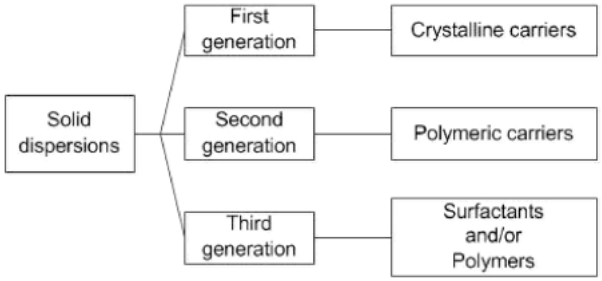
Solid dispersions: Types



(b) α - Solid solution of Y in X
β - Solid solution of X in Y

Solid dispersions: Carrier materials

	hydrophilic	lipophilic
Small molecules	Sugars, sugar alcohols, urea, cyclodextrins, surfactants	Lipids: fats, waxes, paraffins etc., surfactants
Polymers	Macrogols, polyox, cellulose ethers, povidone, copovidone, PEG-PVA graft copolymer etc.	Cellulose ethers, PMMA derivatives, silicones, PE etc.



Solid dispersions: Examples

Brand name	Manufacturer	Drug	Carrier
Gris-PEG	Pedinol Pharmacal Inc.	Griseofulvin	PEG6000
Cesamet	Valeant Pharmaceuticals	Nabilone	PVP
Kaletra	Abbott	Lopinavir, ritonavir	PVPVA
Sporanox	Janssen Pharmaceutica	Itraconazole	HPMC
Intelence	Tibotec	Etravirin	HPMC
Certican	Novartis	Everolimus	HPMC
Isoptin SR-E	Abbott	Verapamil	HPC/HPMC
Nivadil	Fujisawa Pharmaceutical Co., Ltd	Nivaldipine	HPMC
Prograf	Fujisawa Pharmaceutical Co., Ltd	Tacrolimus	HPMC
Rezulin	Developed by Sankyo, manufactured by Parke-Davis division of Warner-Lambert	Troglitazone	PVP

HPMC, hydroxypropylmethylcellulose; HPC, hydroxypropyl cellulose; PVP, polyvinylpyrrolidone; PVPVA, polyvinylpyrrolidone-co-vinylacetate.

Janssens and van den Mooter, 2009

Selection of the polymer

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Safety	Inert
	GRAS (generally recognized as safe)
Preparation	Melting methods:
	Thermally stable
	Thermoplasticity (hot melt extrusion)
	Solvent methods:
	Soluble in organic solvents
Release	Water soluble
	Solubilizing properties
	Stabilizing properties
Stability	High Tg
	High fragility
	Hydrogen donors/acceptors

Janssens and van den Mooter, 2009

Solid dispersions: Advantages

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- Preparation of solid dispersions results in particles with reduced particle size and thus higher surface area and increased dissolution rate is attained. The ultimate result is improved bioavailability.
- Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.
- Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.
- In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.

Vasconcelos et al. (2007)

Solid dispersions: Disadvantages

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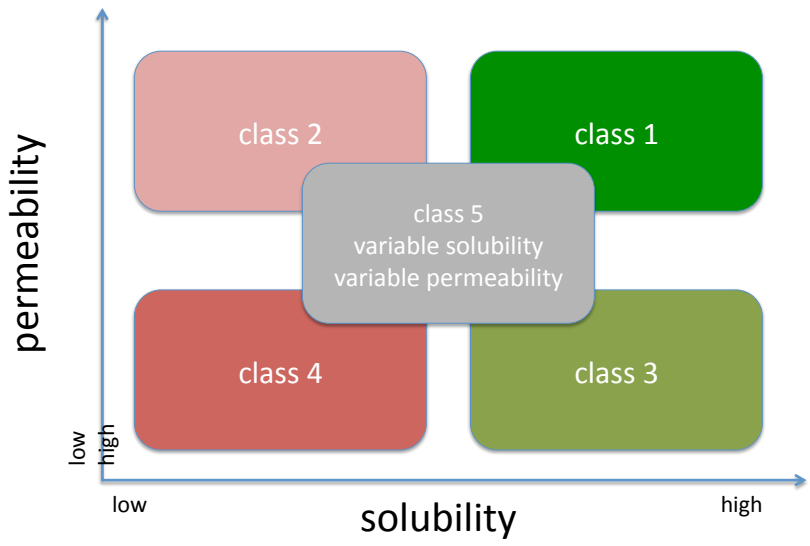
Problems limiting the commercial application of solid dispersions:

- its method of preparation
- reproducibility of its physicochemical properties
- its formulation into dosage forms
- the scale up of manufacturing processes
- the physical and chemical stability of drug and vehicle

Serajuddin (1999)

BCS



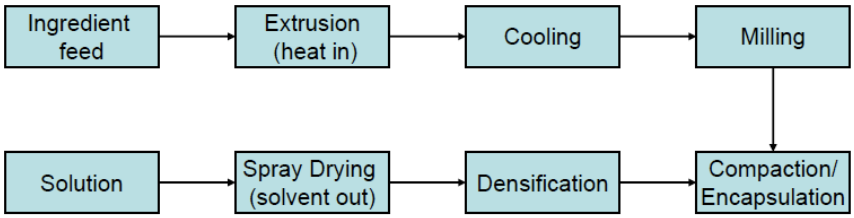
Solid dispersions: Applications

- Increase the aqueous solubility and/ or the dissolution rate and oral bioavailability of the drug substance
- Modify the release of the drug substance by embedding the drug in a matrix
  - Insoluble, inert matrix
  - Soluble or swelling matrix

  →Prolonged dissolution over hours (oral), days, weeks or months (vaginal, parenteral)

Solid dispersions: Production

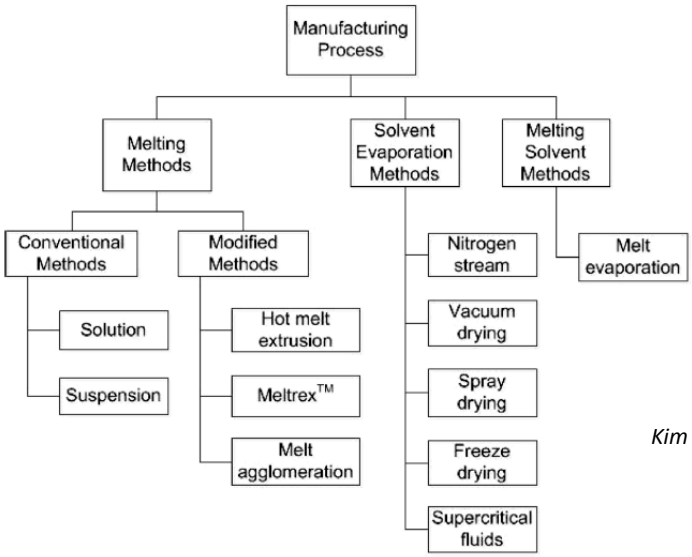
- Solvent methods
  - Spray drying
  - Freeze drying
  - Casting, drying, milling
- Thermal methods
  - Melt extrusion
  - Melt granulation
  - Mixed methods



Solid dispersions: Production

- Solvent methods
  - Viscosity of the solution depends on the concentration and the properties of drug and carrier, e.g. the molecular weight of a polymer.
  - Viscosity is usually low.
- Thermal methods
  - Viscosity of the melt depends on the temperature and the properties of drug and carrier.
  - Viscosity is comparable low for small carrier molecules.
  - High viscosity for polymeric carriers.

Solid dispersions: Production



Kim et al., 2011

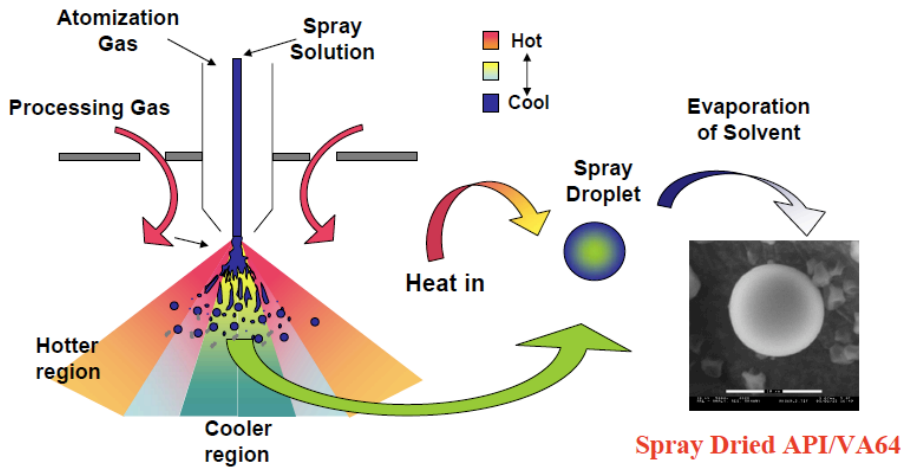
Types of solid dispersion: melting method

- … depends on process conditions and materials
  - – above the melting points of drug and carrier
  - – above the melting point of the carrier but below the melting point of the drug
    → drug dissolves in the carrier
  - – above the melting point of the drug but below the melting point of the carrier
    → drug can plasticize the carrier
  - – below the melting points of drug and carrier

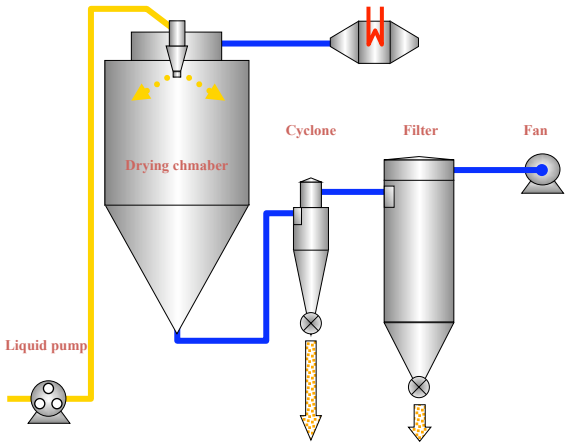
Types of solid dispersion: solvent method

- … depends on process conditions and materials
  - – drug and carrier are soluble in the solvent
    → glassy solid solutions can be formed
  - – carrier is soluble, but drug is not soluble in the solvent
    → two phase systems will be formed

Spray drying



Spray dryer



Cyclone

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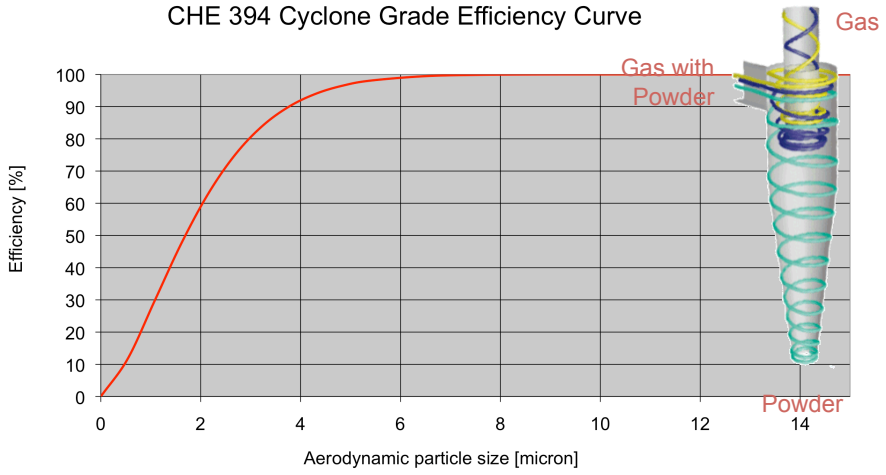

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Thermal Energy Flow in Spray Dryer

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Inlet drying air:

Temperature:	200	° C
Flow:	1250	kg / h
Vapour content:	10	g / kg
Air enthalpy:	70	kW
Vapour enthalpy:	10	kW
Total enthalpy:	**80**	**kW**

Feed:

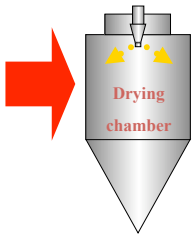
Temperature:	20	° C
Flow:	63	kg / h
Water content:	75	%
Total enthalpy:	**1,2**	**kW**

Evaporation:

Rate:	46	kg / h

Q_{in} = 81,2 kW

$Q_{in} = Q_{out}$



Outlet drying air:

Temperature:	90	° C
Flow:	1296	kg / h
Vapour content:	47	g / kg
Air enthalpy:	31	kW
Vapour enthalpy:	44	kW
Total enthalpy:	**75**	**kW**

Powder:

Temperature:	85	° C
Flow:	16,5	kg / h
Water content:	5	%
Total enthalpy:	**0,6**	**kW**

Heat loss:

Total enthalpy:	**5,6**	**kW**

Q_{out} = 81,2 kW

1 kJ is required to heat 1 kg of air by 1 °C
To evaporate 1 kg of water 2400 kJ are required

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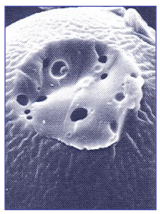
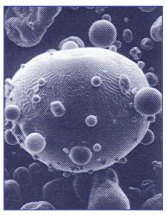
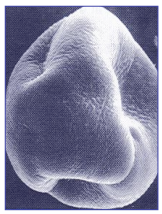
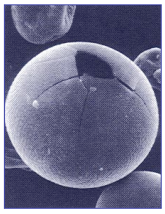
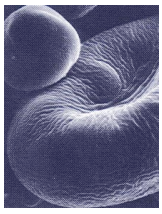
Spray drying products

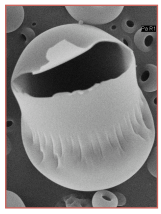

Solid particle


Solid particle with satellites


Shrivelled particle


Hollow particle


Cenosphere


Disintegrated particle

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Solid dispersions: Miscibility and Solubility

- Miscibility describes the tendency of the supercooled liquid/glassy form of the API to mix with a polymer.
- Solubility refers to the ability of the polymer to act as a "solvent'' and dissolve a crystalline API.
- Appearance of crystalline API in a solid dispersion following manufacturing or storage does not necessarily imply that the two liquids are immiscible.
- Crystalline API can also be explained if the solubility limit has been exceeded and conditions were favorable for crystallization.

Marsac et al. 2006

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Solid dispersions: Miscibility and Solubility

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- If the solubility of the API in the polymer can be measured or estimated, then the degree of supersaturation, which is a measure of the driving force for crystallization can be evaluated.

Marsac et al. 2006

Solid dispersions: Miscibility and Solubility

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- The term miscibility is used to refer to the formation of a single phase amorphous system through liquid/liquid mixing where one liquid is an amorphous polymer and the other liquid is an amorphous drug (clearly this is an oversimplification for systems below the glass transition temperature since these are non-equilibrium).
- Molecular level mixing can be achieved either by dissolution of each component in a mutual solvent followed by solvent removal or by directly mixing the two liquids.

Marsac et al. 2006

Solid dispersions: Miscibility and Solubility

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- Thermodynamics dictate that metastable/unstable systems will tend to phase separate but due to slow dynamics, the blend may be sufficiently kinetically stable for the intended use.

Marsac et al. 2006

Solid dispersions: Miscibility and Solubility

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- In order to modify the physical stability of the drug, molecular level mixing with the polymer is desirable, thereby altering the local environment of the drug.
- If the two components are immiscible, the properties of the pure amorphous solid will largely dominate the crystallization behavior of the mixture and effects of the polymer on physical stability will be limited.
- The chemical potential of the API will be lowered through mixing with a polymer. Reducing the chemical potential will alter the thermodynamic driving force for crystallization.

Marsac et al. 2006

Solid dispersions: Solubility

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- Solubility measurements
- Solubility parameters
- Flory-Huggins modeling

Marsac et al. 2006

Strategies to avoid recrystallisation

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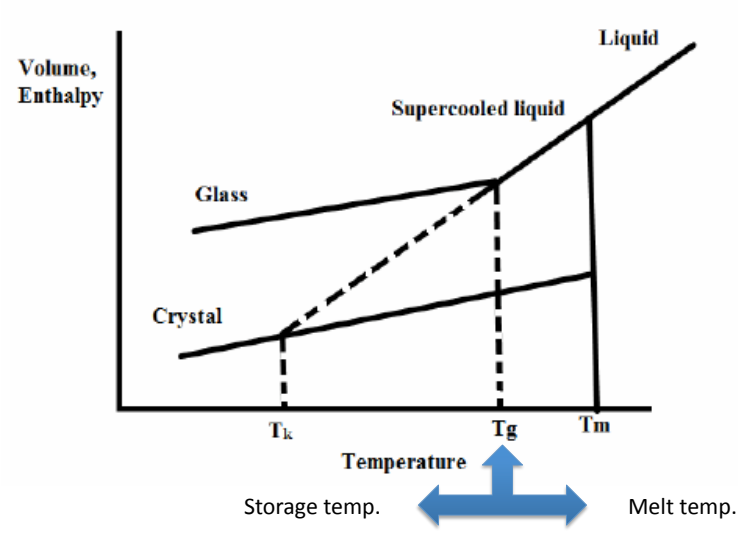
- Reduction of molecular mobility
  - T_g >50K above storage temperature
  - high interactions between polymer and drug
    - Hydrogen bonds
    - Electrostatic interaction (e.g. salt formation)
- High conformational entropy of the solid dispersion

Solid dispersions: Properties

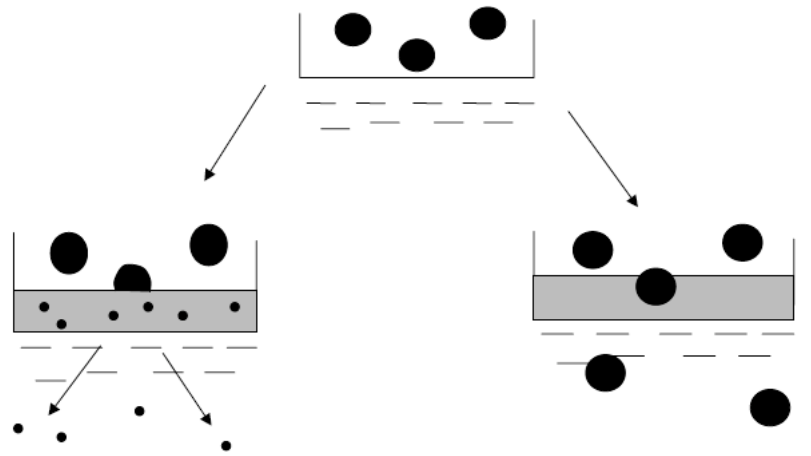


Selection of the polymer

Safety	Inert
	GRAS (generally recognized as safe)
Preparation	Melting methods:
	Thermally stable
	Thermoplasticity (hot melt extrusion)
	Solvent methods:
	Soluble in organic solvents
Release	Water soluble
	Solubilizing properties
	Stabilizing properties
Stability	High Tg
	High fragility
	Hydrogen donors/acceptors

Janssens and van den Mooter, 2009

Solid dispersions: Dissolution



Carrier controlled dissolution

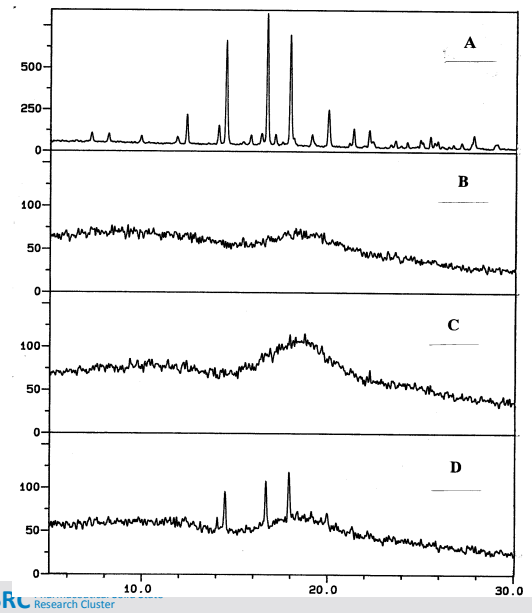
Drug controlled dissolution

Craig 2002

Solid dispersions: Characterisation

- XRPD
- (modulated) DSC
- TMA, DMA
- Hot stage microscopy
- SEM, TEM
- Spectroscopic methods
  - IR
  - Raman
- SS-NMR

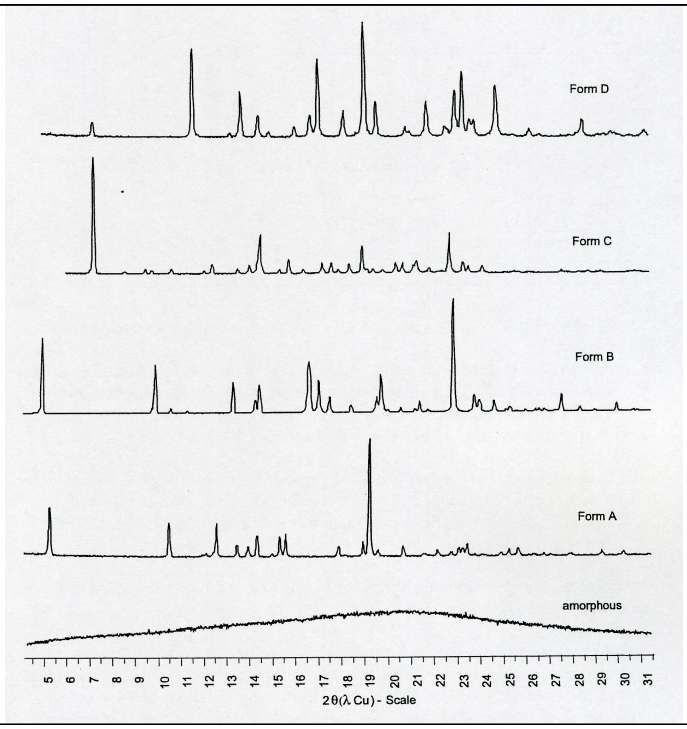
XRPD



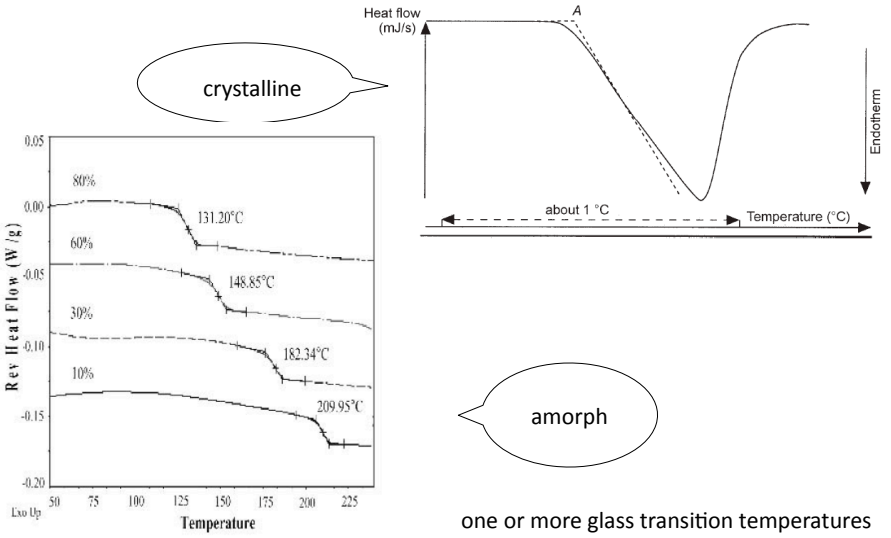
crystalline

amorph

partly crystalline



DSC



one or more glass transition temperatures

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Gordon-Taylor equation

- Prediction of the glass transition temperature of glassy solid solutions of drug and carrier

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2}$$

w_i	*weight fractions of the components*
K	*parameter*
ρ_i	*densities of the amorphous components*
subscript $_2$	*compound with the higher Tg*
ΔCp_i	*heat capacity change*

Simha-Boyer rule

$$K \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2}$$

Couchman-Karasz equation

$$K = \frac{\Delta Cp_2}{\Delta Cp_1}$$

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DSC

Melting point depression
Marsac et al. 2006

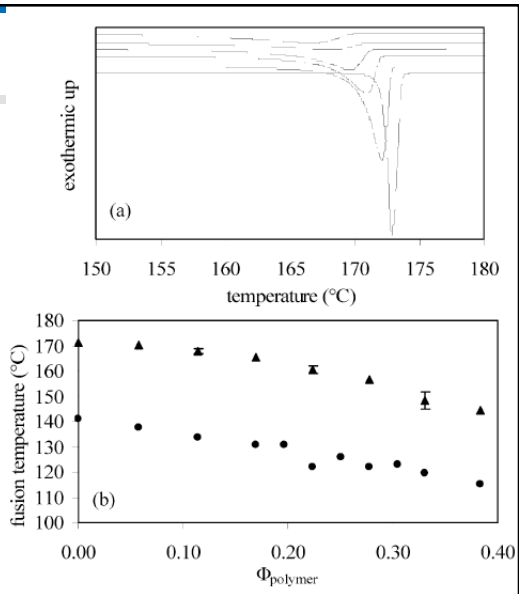

Fig. 3. DSC thermograms of physical mixtures of nifedipine and 0, 5, 10, 15, and 25wt.% PVP K12 measured at a heating rate of 1°C/min (a). Extrapolated onset of melting of nifedipine (▲) and felodipine (●) as a function of volume fraction of PVP K12 (b).

DSC

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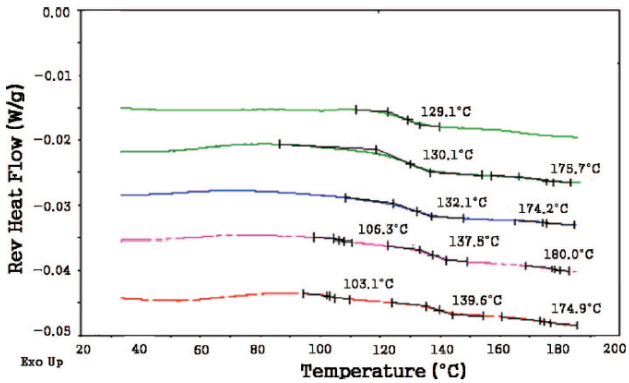
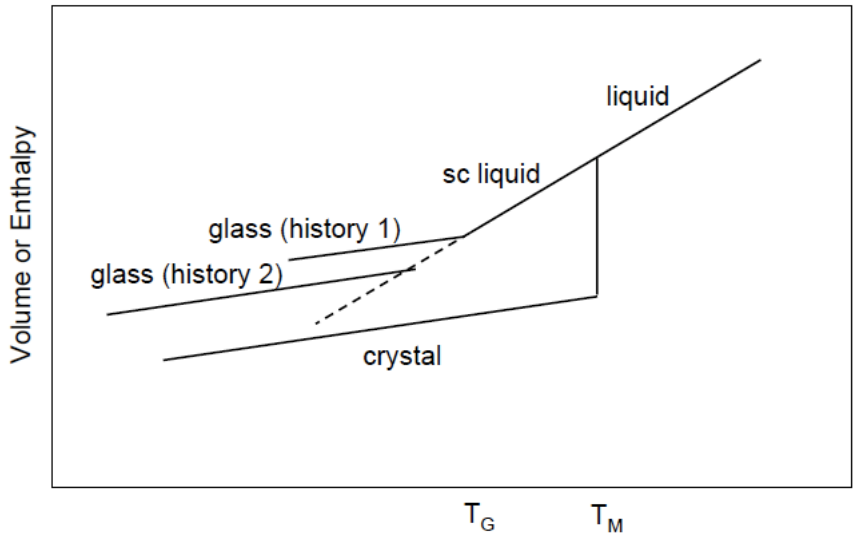


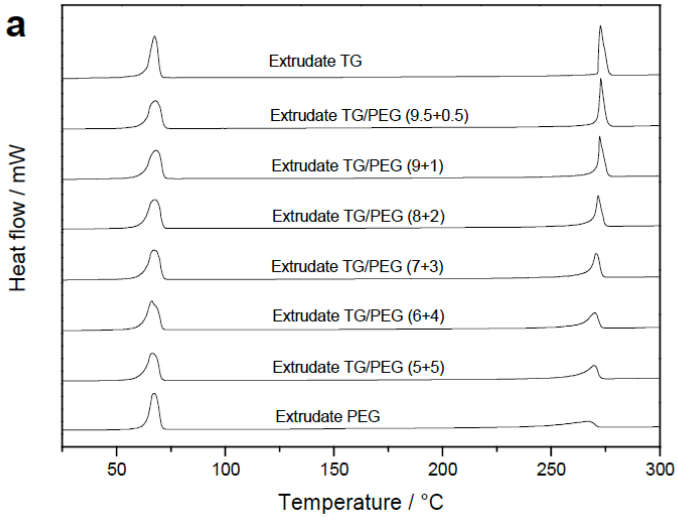
Figure 10. MDSC of 30% compound I melt extrudates stored over 12 months at various conditions. The storage conditions from top to bottom are 25 °C/60% RH, 1 month; 25 °C/60% RH, 3 months; 25 °C/60% RH, 12 months; 40 °C/75% RH, 6 months; and 40 °C/75% RH, 12 months.

Phase separation during storage: one T_g after production -> more T_gs after storage
Lakshman 2008

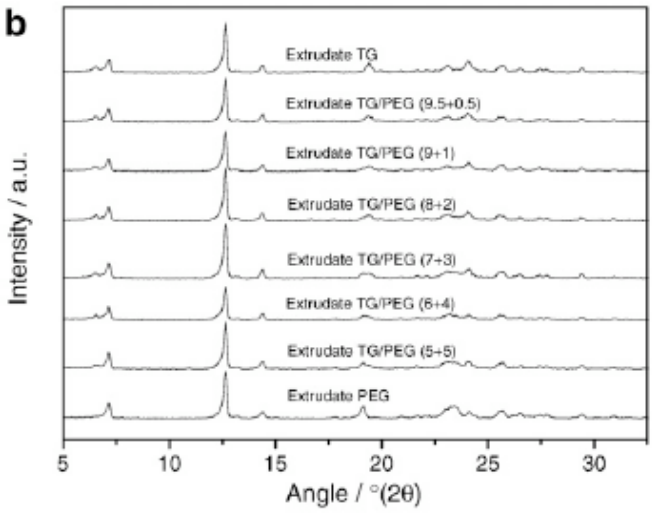
History of product



Tripalmitin/ Macrogol 10.000: DSC



Tripalmitin/ Macrogol 10.000: XRPD



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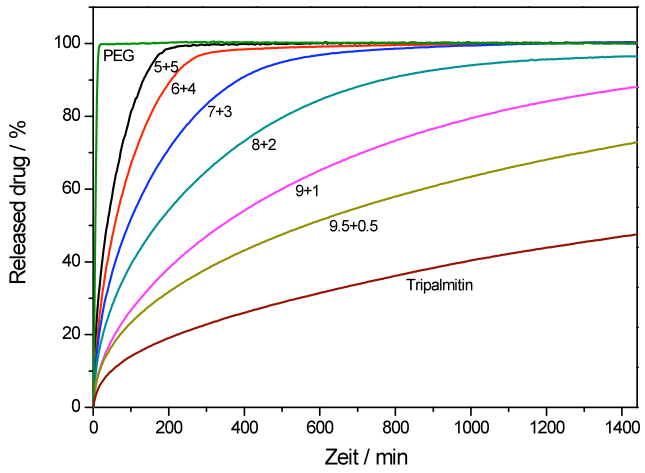
Release from Mixed Matrices



Basket, 242 nm, 37±0,5 °C, 50 rpm, pur. water, n=3, mean, SD<4%, not shown

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Hot stage microscopy

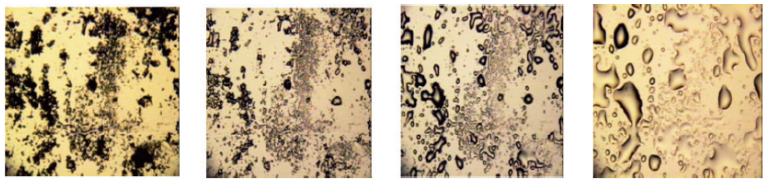

Figure 2. Appearance of amorphous compound **I** under hot-stage microscope at 25 °C, 120 °C, 126 °C, 140 °C (from left to right).

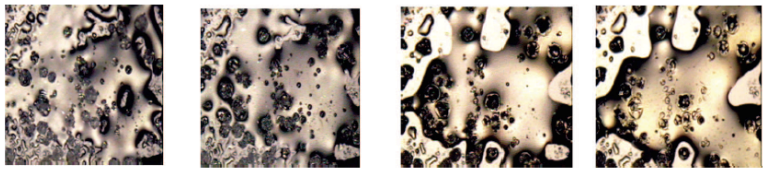

Figure 3. Appearance of physical mixtures of compound **I** and PVP K-30 under hot-stage microscope at 120 °C, 140 °C, 155 °C, 170 °C (from left to right) when powders of PVP-K30 are added to amorphous **I** on the glass slide.

Drug liquefies around T_g of 125°C; 10% of PVP K-30 dissolvs in the drug reducing the T_g of the polymer
Lakshman 2008

References

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- PJ Marsac, SL Shamblin, LS Taylor: Theoretical and Practical Approaches for Prediction of DrugYPolymer Miscibility and Solubility. Pharm Res 2006; 23: 2417-2426

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