LIQUISOLID SYSTEMS

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MUNI
PHARM

Lecture content

1. Bioavailability and its increasing
2. Liquisolid systems characterization
3. Excipients for LSS
4. Preformulation studies of LSS
5. Evaluation methods for LSS
6. LSS practical application and research

Bioavailability of the drug

- **Defined as the amount of the drug and the overall speed/rate and extent of the process by which the API of the administered dose reaches the site of action/the systemic blood circulation**

Factors affecting bioavailability after oral administration

- physico-chemical API´s properties (c, Mw, hydro/lipo-philic, pKa)
- organism factors (conditions in GIT - motility, pH, surface area, blood supply, enzymes, etc.)
- dosage/medical/application form
- food intake
- intra-individual changes (biorhythms, illnesses)
- inter-individual changes (sex, age, enzymes)

"Galenic availability" → **release rate**, **dissolving of API in GIT**, **absorption**

The U. S. Food and Drug Administration, www.fda.gov
ALLAM, A.N., EL GAMAL, S.S., NAGGAR, V.F.: Bioavailability: A Pharmaceutical Review. Int J Nov Drug Deliv Tech. 2001; 1, 80-96.

Bioavailability of the drug

Main reasons of insufficient bioavailability

- Limited solubility of the drug
- Insufficient permeability throw biological membranes
- Short time for absorption
- Degradation of API in the GIT
- First-pass effect

HETAL, T., BINDESH, P., SNEHA, T.: A review on techniques for oral bioavailability enhancement of drugs. Int J Pharm Sc Rev Res. 2010; 4, 203-223.

Drug solubility

- important parameter influencing the desired concentration of API in systemic circulation capable of eliciting the expected pharmacotherapeutic response
- defined as concentration of saturated solution (the amount of a solute that passes into solution).

Descriptive term	Approximate volume of solvent in millilitres per gram of solute			
Very soluble	less than	1		
Freely soluble	from	1	to	10
Soluble	from	10	to	30
Sparingly soluble	from	30	to	100
Slightly soluble	from	100	to	1000
Very slightly soluble	from	1000	to	10 000
Practically insoluble	more than			10 000

- from a pharmacological perspective, the division is usually inadequate since there is not reflected therapeutic dose

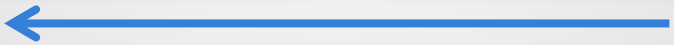
Biopharmaceutical Classification System (BCS)

1st group
(good solubility,
good permeability)
caffeine, diazepam, enalapril, lidocaine

2nd group
(bad solubility,
good permeability)
atorvastatin, diclofenac, indomethacin, warfarin

3rd group
(good solubility,
bad permeability)
amoxicillin, atenolol, codeine, metformin

4th group
(bad solubility,
good permeability)
furosemide, neomycin, hydrochlorothiazide



- **well-soluble drugs** - highest **dose** could be dissolved in 250 ml aqueous buffer (pH 1-8), **highly permeable** substance have a degree of absorption from the GIT at least 90%
- 40% of used drugs (up to 70% of newly synthetized APIs) → BCS groups II. or IV. → problems during oral SDF formulation

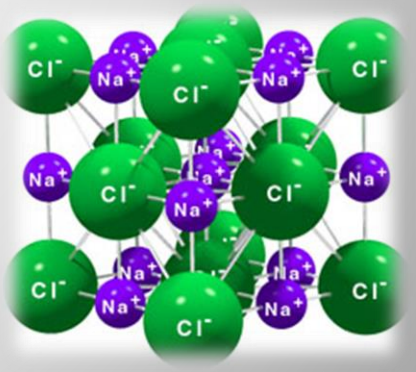
Bioavailability | **Characterization of LSS** | **Excipients** | **Preformulation studies** | **Evaluation methods** | **LSS application**

AMIDON, G.L., LENNEMÄS, H., SHAH, V.P., et al.: A theoretical basis for a bioapharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12, 413-420.

Bioavailability increasing

Chemical methods of API modification

- Salts
- Hydrates
- Glycosylated derivatives
- Pro-drugs
- Chelation phenomenon



Bioavailability increasing

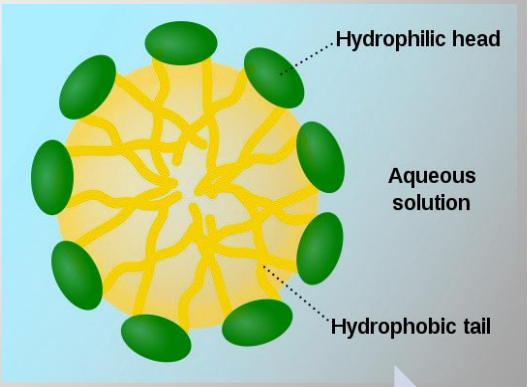
Physical and technological methods

- Crystalline polymorph or amorph, co-crystals
- Controlled crystallization (sonocrystallization, crystallization from SCF)
- Lyophilization
- Spray drying
- API micronization (milling)
- Nanonization
- Facilitated dissolving
- Improvement of wettability
- Micelar solubilization
- Hydrotropism phenomenon

Bioavailability increasing

Physical and technological methods

- Preparing of cyclodextrin complexes
- pH change
- Solid dispersion preparing
- Using of interactive powder mixtures
- Micrognanulation
- Impregnation
- SEDDS
- Micro- and nano-suspensions
- Nanoparticles
- Liposomal formulations
- Absorption enhancers usage
- Formulation of liquisolid systems



Liquisolid systems - description

- modern preparations with ability to **increase bioavailability** of badly soluble APIs (II. and IV. BCS)
- technological improvement of powdered solutions
- the principle lies in **sortion of API in liquid state** using mixing/spraying **onto highly-porous carrier**, which is subsequently coated by material with high specific surface area – **LSS**

KULKARNI, A.S., ALOORKAR, N.H., MANE, M.S., et al.: Liquisolid Systems: A Review. Int J Pharm Sci Nanotech. 2010; 3, 795-802.
NAGABANDI, V.K., RAMARAO, T., JAYAVEERA, K.N.: Liquisolid Compacts: A Novel Approach to Enhance Bioavailability of Poorly Soluble Drugs. Int J Pharm Biol Sci. 2011; 1, 89-102.

Liquisolid systems – adv. vs. disadv.

- Improved bioavailability of API
- Final processing similar to conventional DF

- Low manufacturing cost
- Minimized influence of pH on drug release
- Possibility to prepare DF with accelerated, conventional and controlled-release (tbl., cps., ODT)

Liquisolid systems – limits

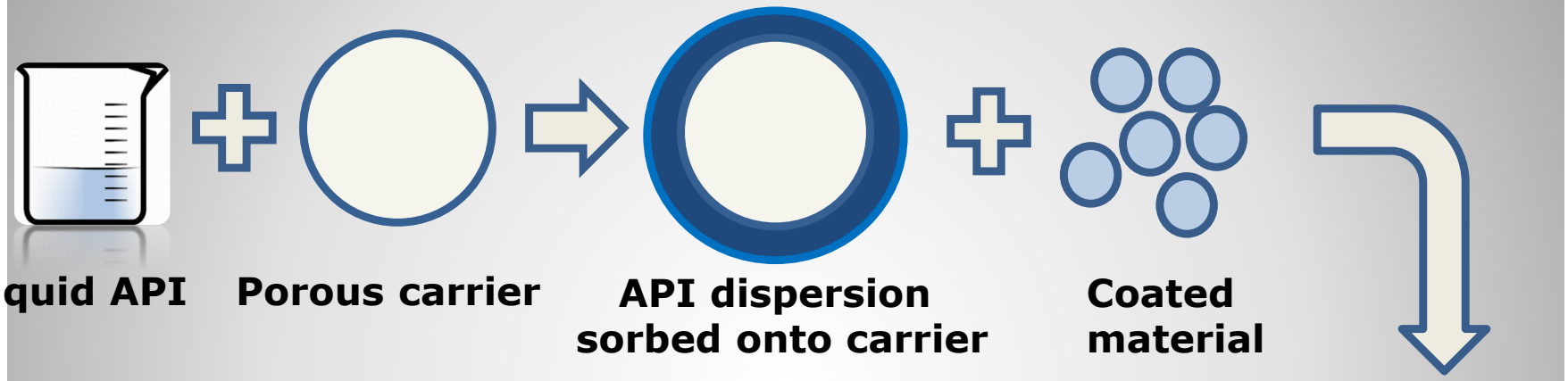
- The solubility of the drug in the non-volatile solvent
- The size of the final DF
- Limited number of excipients + price
- Mechanical properties of DF (liquid squeezing out)

Liquisolid systems – mechanism

- Large surface area of carrier → easy drug release
- Better wetting of DF surface
- API is in LSS dissolved → eliminating one of the most limiting systemic absorption steps - dissolving in the GIT

FAHMY, R.H., KASSEM, M.A.: Enhancement of famotidine dissolution rate through liquisolid tablets formulation: In vitro and in vivo evaluation. Eur J Pharm Biopharm. 2008; 69, 993-1003.
SAMBASIVA, R., NAGA, T.A.: Liquisolid technology: An Overview. Int J Res Pharm Biomed Sci. 2011, 2, 401-409.

Liquisolid systems – preparation



Liquid API

Porous carrier

API dispersion sorbed onto carrier

Coated material

Final dosage form

Other excipients

Liquisolid powder

Bioavailability | Characterization of LSS | Excipients | Preformulation studies | Evaluation methods | LSS application

Liquisolid systems – excipients

Solvent

- Non-volatile
- Hydrophilic (if possible)
- High-boiling point, low viscosity

- Fast (enhanced) drug release → high dissolving capacity of API
- Controlled (delayed, prolonged) release → low dissolving

PEG, *propylene glycol*, *glycerol*, *polysorbates*...

JAVADZADEH, Y., MUSAALREZAEI, L., NOKHODCHI, A.: Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm. 2008; 362, 102-108.

Liquisolid systems – excipients

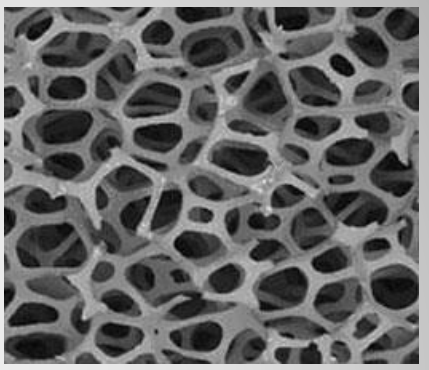
Solvent

- Solvent has a significant impact on LSS properties (release rate, mechanical durability, etc.) and influences also API´s bioavailability

The principle of LSS preparing enables except **solvents miscible with water** (allowing administration of already dissolved drug), also use of **lipophilic solvents** and **surfactants** (tensides/surface active agents), which could be sorbed onto the porous carrier to form the self-emulsifying system, providing increased bioavailability of certain drugs (digestion of fats).

Liquisolid systems – excipients

Carriers



- Porous materials
- High-sorptive capacity
- Influence processability, behavior and size of final product/DF
- Non-toxic, stable

- *MCC; aluminometasilicates (Neusilin); saccharides; hydrogencarbonates Ca, Mg; hydrogenphosphate Ca (Fujicalin)*

Fuji Chemical Industry Co., Ltd. (2009). The Specialty Excipient Neusilin® [WWW] Fuji Chemical Industry Co., Ltd. Available from: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Neusilin.pdf

Liquisolid systems – excipients

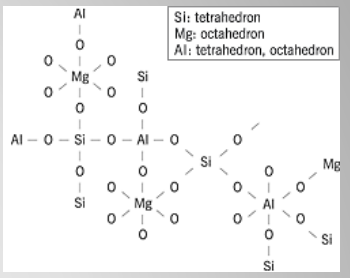
Classification of carriers into four categories and their SSA

Carrier category	Carrier	SSA [m^2/g]
Cellulose and cellulose derivatives	microcrystalline cellulose	~1.18
	hydroxypropyl methylcellulose[a]	-
Saccharides	lactose	~0.35
	sorbitol	~0.37
Silicates	magnesium aluminometasilicate	110–300
	kaolin	~24
	diosmectite	–
	ordered mesoporous silicates	up to 1500
Others	anhydrous dibasic calcium phosphate	30
	polymethacrylates[a]	–
	starch	~0.60
	magnesium carbonate	~10

[a] Carrier material for LSS with controlled drug delivery

VRANÍKOVÁ, B., GAJDZIOK, J.: Liquisolid systems and aspects influencing their research and development. Acta Pharmaceutica. 2013; 63, 447-465.

Liquisolid systems – excipients

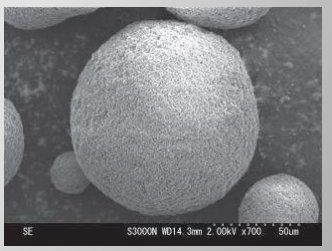


Neusilin®

- magnesium aluminometasilicate
- specific surface area 110 - 300 m^2/g
- 4 (11) types (agglomerated x powder; pH – antacid)

Use:

- Direct compression – improve flowing properties, compressibility, hardness
- Wet granulation
- Solid dispersions
- Improves stability of moisture sensitive drugs
- Solid SEDDs
- **Carriers and coating materials for LSS**



Fuji Chemical Industry Co., Ltd. (2009). The Specialty Excipient Neusilin® [WWW] Fuji Chemical Industry Co., Ltd. Available from: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Neusilin.pdf

Liquisolid systems – excipients

Type	Loss of drying (%)	Bulk density (g/ml)	Tapped density (g/ml)	Tru density	SSA (m^2/g)	Particle size (μm)	Angle of repose (°)	Adsorption capacity (ml/g)	pH 5% suspension
NFL2N	<5	0.08-0,13	0.14-0.20	2.2	250	-	45	2.0-2.4	6.5-8.0
NS2N	<5	0.17-0,25	0.20-0.33	2.2	250	44-177	30	2.0-2.4	6.5-7.5
US2	<7	0.13-0,18	0.16-0.22	2.2	300	44-177	30	2.7-3.4	6.0-8.0
UFL2	<7	0.06-0,11	0.10-0.17	2.2	300	-	45	2.7-3.4	6.0-8.0
FH1	13-20	0.27-0,34	0.36-0.45	2.0	110	-	45	1.3	8.5-10.0
FH2	<5	0.25-0,33	0.34-0.48	2.2	110	-	45	1.5	8.5-10.0
FL1	13-20	0.15-0,19	0.23-0.29	2.0	150	-	42	1.4	8.5-10.0
FL2	<5	0.15-0,19	0.22-0.29	2.2	150	-	45	1.5	8.5-10.0
S1	13-20	0.30-0,37	0.36-0.43	2.0	110	44-250	30	1.3	8.5-10.0
S2	<5	0.29-0-37	0.34-0.42	2.2	110	44-250	30	1.4	8.5-10.0
SG2	8-12	0.30-0,37	0.33-0.42	2.1	110	125-500	25-32	1.4	8.5-10.0

Fuji Chemical Industry Co., Ltd. (2009). The Specialty Excipient Neusilin® [WWW] Fuji Chemical Industry Co., Ltd. Available from: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Neusilin.pdf [staženo 18. dubna 2015]

Liquisolid systems – excipients

Neusilin®

General Properties of Neusilin

Appearance	White powder or granules
Physical Form	Amorphous
True Specific Gravity	2.0-2.2
Solubility	Practically insoluble in water and in ethanol
Composition (%) on Dried Basis	Al_2O_3 – 29.1 – 35.5 MgO - 11.4 – 14.0 SiO_2 - 29.2 - 35.6
Loss on Drying	Less than 20 to 5% depending on grades
CAS Number	12511-31-8
EINECS Number	235-682-0

Typical Properties

GRADE		Alkaline		Neutral	
		S1	S2	UFL2	US2
Appearance		White granule	White granule	White powder	White granule
Degree of whiteness (%)		>95	>95	>95	>95
Loss on drying (%) 110°C, 7 hours		13 - 20	< 5	<7	<7
Bulk density	Loose (g/ml)	0.30 - 0.37	0.29 - 0.37	0.06 - 0.11	0.13 - 0.18
	Tapped (g/ml)	0.36 - 0.43	0.34 - 0.42	0.10 - 0.17	0.16 - 0.22
True specific gravity		2.0	2.2	2.2	2.2
Specific surface area (m^2/g)*1		110	110	300	300
Average particle size (μm)		112	115	3.1	106
Angle of repose (°)		30	30	45	30
Oil adsorbing capacity (ml/g)*2		1.3	1.4	2.7 - 3.4	2.7 - 3.4
Water adsorbing capacity (ml/g)		1.0	1.2	2.4 - 3.1	2.4 - 3.1
Acid consuming capacity (ml/g)*3		≧210	≧210	≧210	≧210
pH (4% slurry)*4		8.5 - 10.0	8.5 - 10.0	6.0 - 8.0	6.0 - 8.0

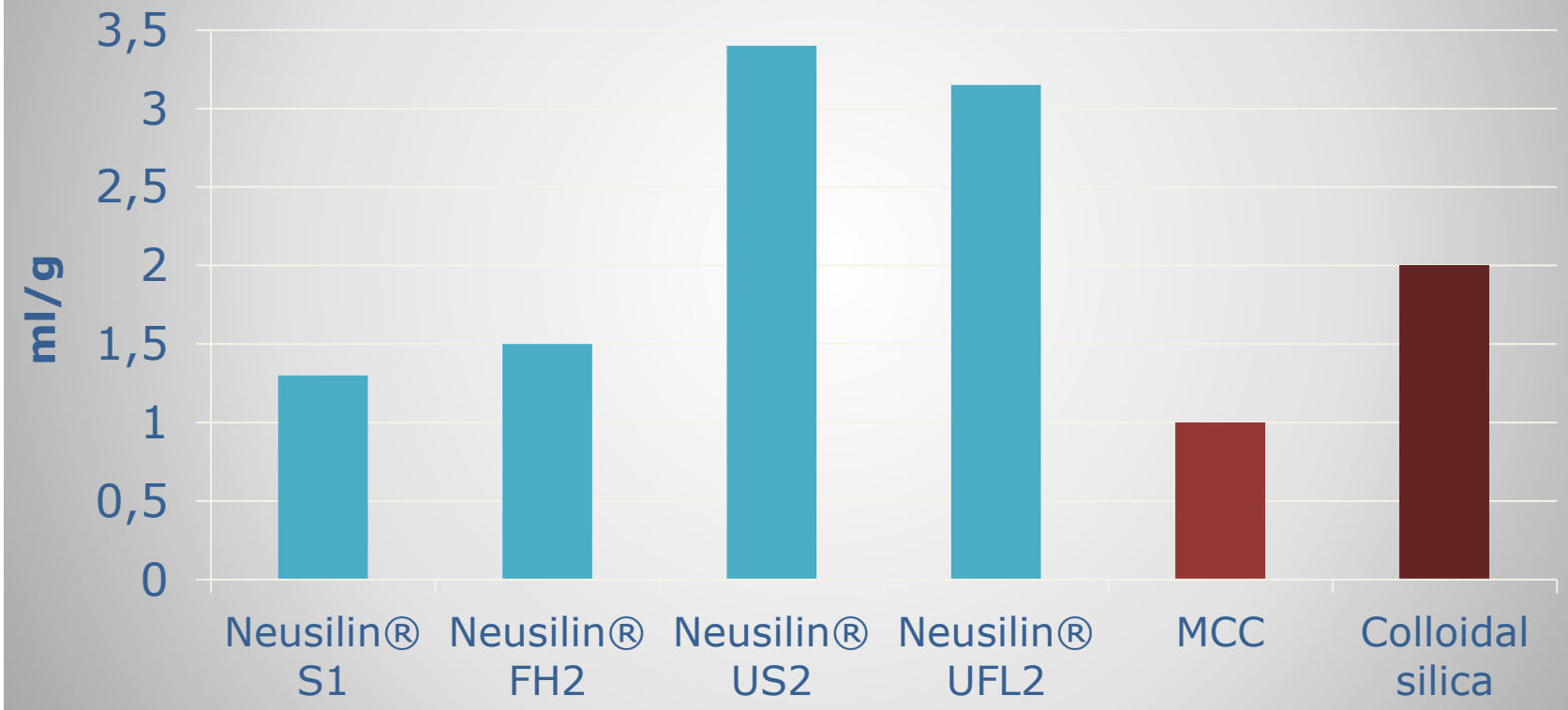
Neusilin Grades

UFL2	US2	S1	S2
Neutral	Neutral	Alkaline	Alkaline
Powder	Granule	Granule	Granule
Low water	Low water	High water	Low water

Fuji Chemical Industry Co., Ltd. (2009). The Specialty Excipient Neusilin® [WWW] Fuji Chemical Industry Co., Ltd. Available from: http://www.harke.com/fileadmin/images/pharma/Broschueren/Fuji_Neusilin.pdf

Liquisolid systems – excipients

Absorption capacity of some grades of Neusilin in comparision to other used materials



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Liquisolid systems – excipients

Neusilin®

- Adsorption properties are utilized e.g. in the tobacco industry - added to cigarette filters to absorb aldehydes
- In FT - used as carriers in the preparation of solid dispersions in order to increase the solubility of API; granulation of oil formulations and to improve the stability of some products
- Alkaline Neusilins are used as antacids (JP) with maximum dose 4 g/day
- For LSS/S(m)EDDS most often used US2 (agglomerated type) (≈ 300 m^2/g; 3,4 ml/g)

Liquisolid systems – excipients

Coating material

- Fine particles (0.01 – 5 μm)
- High-sorptive properties
- High SSA

- Infuence mixture flowing properties, bind excess liquid from the carrier surface

- Cannot be used as carriers → poor flowing and compressible properties

- *Colloidal silicon dioxide (silica), powdered magnesium aluminometasilicates, calcium silicate*

NOKHODCHI, A., ALIAKBAR, R., DESAI, S., et al.: Liquisolid compacts: The effect of cosolvent and HPMC in theophylline release. Colloid Surface B: Biointerdaces, 2010; 79, 262-269.

Liquisolid systems – excipients

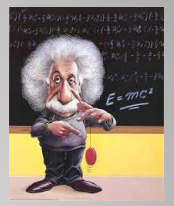
Others

- Disintegrants – superdisintegrants (cross-povidone, cross-carmellose, starches)
- Lubricants and antiadhezives (talc, magnesium stearate)
- Fillers (lactose, MCC, calcium carbonate, etc.)

NOKHODCHI, A., ALIAKBAR, R., DESAI, S., et al.: Liquisolid compacts: The effect of cosolvent and HPMC in theophylline release. Colloid Surface B: Biointerdaces, 2010; 79, 262-269.

Liquisolid systems – theoretical aspects

Preformulation studies



- necessary for obtaining powdered mixtures with suitable flow properties and subsequently preparing the final formulation that meets all the requirements for tablets, capsules or granules

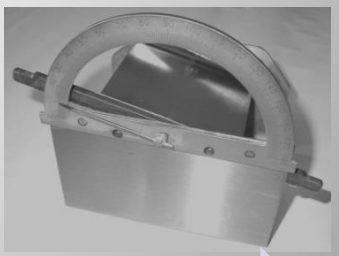
- related to the selection of a suitable solvent to disperse the drug and calculating the amount of powder excipients - carrier and coating material

Liquisolid systems – theoretical aspects

Preformulation studies

- Drug solubility
  - preparing a saturated solution by adding an excess of tested API to various solvents
  - after equilibration, the amount of dissolved active ingredient is quantified by suitable analytical method

- Angle of slide (~ 33 °)
  - specific test used to evaluate flow properties of powders
  - optimum about 33 °



Liquisolid systems – theoretical aspects

Preformulation studies

- Drug solubility
- Angle of slide (~ 33 °)
- Calculation of the amount of carrier and coating material

$$\Phi_{CA} = \frac{max\ W}{Q} \quad \textbf{or} \quad \Phi_{CO} = \frac{max\ W}{q}$$

$$\psi_{CA} = \frac{max\ W}{Q} \quad \textbf{or} \quad \psi_{CO} = \frac{max\ W}{q}$$

$$L_f = \Phi_{CA} + \frac{\Phi_{CO}}{R} \quad \textbf{and} \quad L_f = \psi_{CA} + \frac{\psi_{CO}}{R}$$

$$L_{f\,\text{optimal}} = \frac{W}{Q} \qquad R = \frac{Q}{q} \quad \textbf{(10:1-100:1)}$$

Q	amount of carrier (g)
q	amount of coating material (g)
W	amount of drug in liquid state
Φ	flowable liquid retention potential for carrier/coated material
Ψ	compressible liquid retention potential for carrier/coated material
Lf	liquid load factor – flowable/compressible

SPIREAS, S, BOLTON, S.M.: Liquisolid systems and methods of preparing same. US6423339, 2002.

Liquisolid systems – theoretical aspects

DETERMINING of the FLOW RETENTION POTENTIAL

$$\Phi_{CA} = \frac{max\ W}{Q\ (q)}$$

- capacity of the powder for retention a specific amount of liquid phase in its structure, while maintaining acceptable flow properties
- the quantity of liquid in grams that can be sorbed onto a powder (the carrier or coating material), while maintaining acceptable flow properties of the mixture

Powder excipients are mixed with varying amounts of liquid and angle of slide of these mixtures is measured (also other flow characteristics).

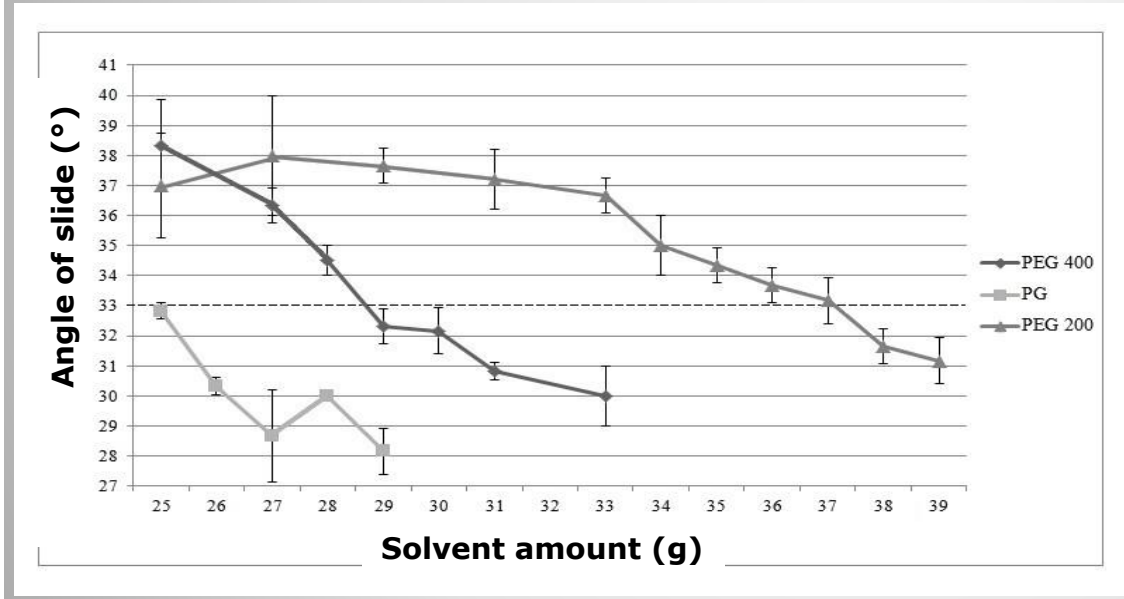
The ratio liquid/solid with angle of slide 33 ° is taken as Φ value.

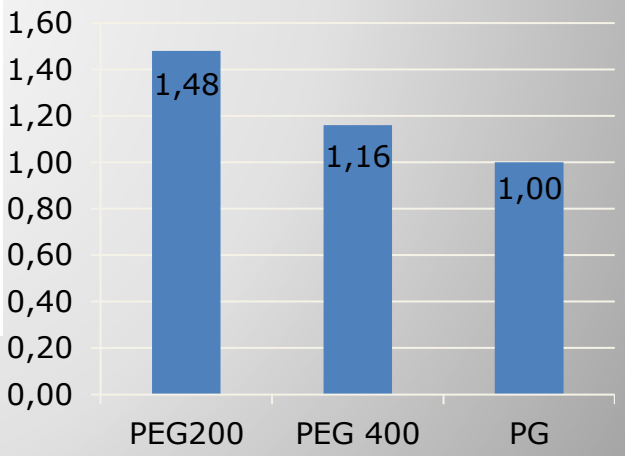
Similarly, the compression parameters (squeezing out)!

SPIREAS, S, BOLTON, S.M.: Liquisolid systems and methods of preparing same. US6423339, 2002.

Liquisolid systems – theoretical aspects

DETERMINING of the FLOW RETENTION POTENTIAL of Neusilin US2 for PG, PEG 200 a PEG 400

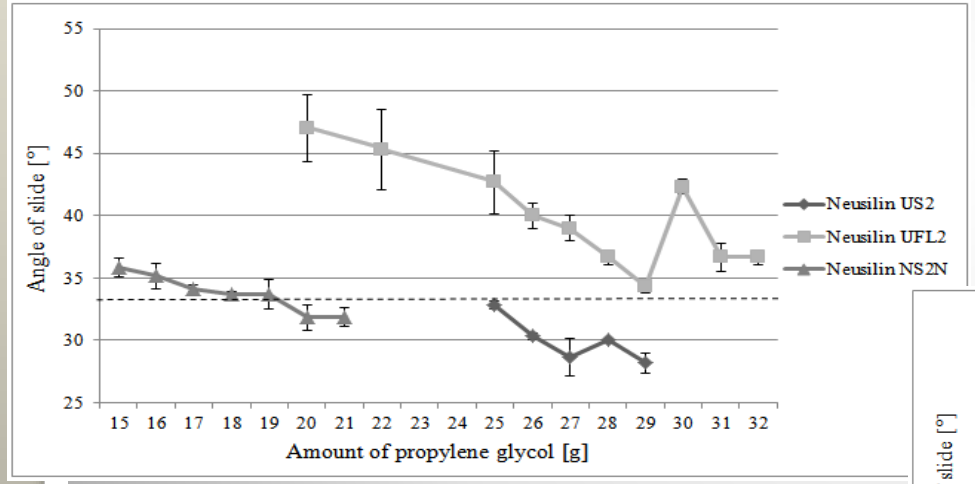


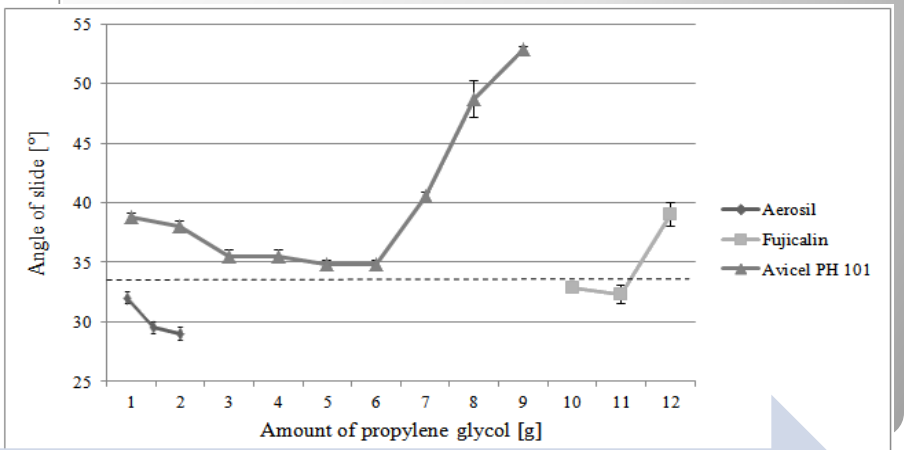


VRANÍKOVÁ, B., J. GAJDZIOK a D. VETCHÝ. Determination of flowable liquid retention potential of aluminometasilicate carrie for liquisolid systems preparation. Pharmaceutical Development and Technology. 2015, 20(7): 839-844. ISSN 1083-7450.

Liquisolid systems – theoretical aspects

DETERMINING of the FLOW RETENTION POTENTIAL of carriers (MCC, Fujicalin, Neusilin US2 a NS2N) and coating materials (Aerosil 200 a Neusilin UFL2) for PG





Bioavailability | Characterization of LSS | Excipients | Preformulation studies | Evaluation methods | LSS application

Liquisolid systems – theoretical aspects

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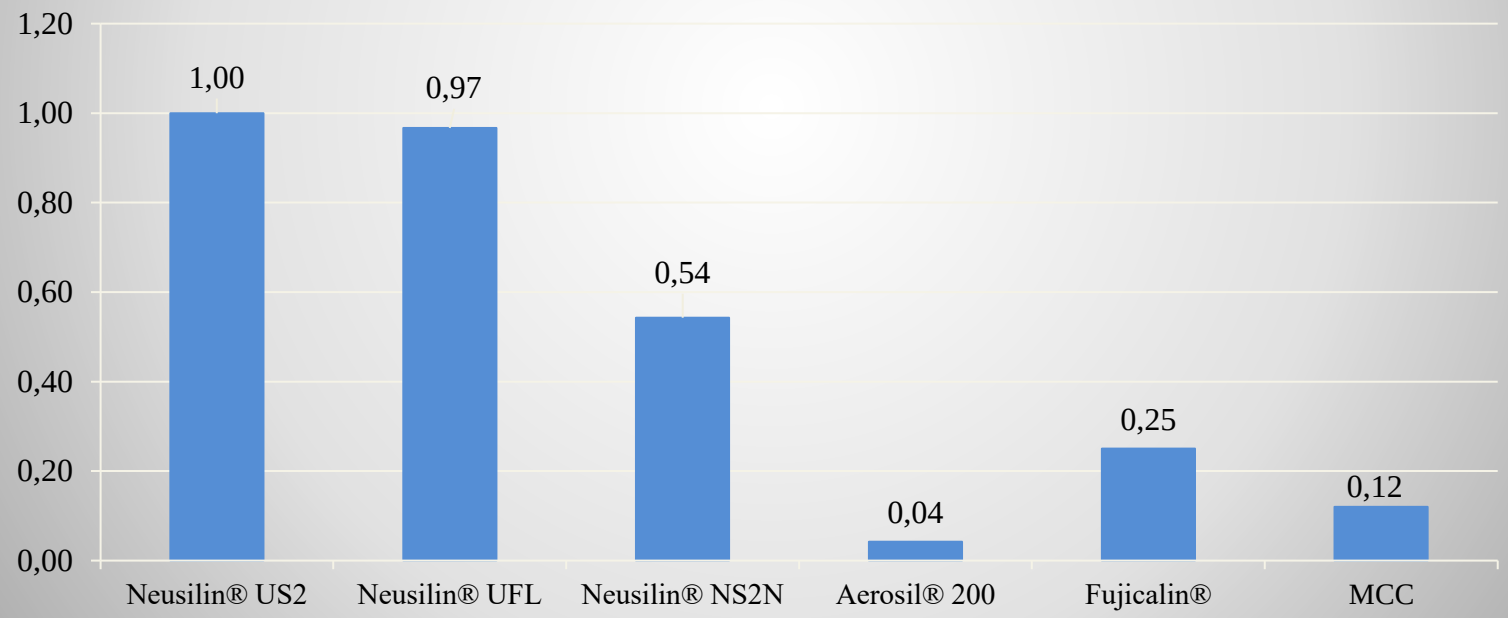
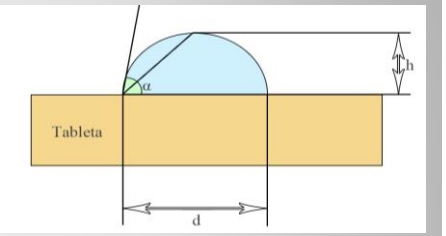


VRANÍKOVÁ, B. a J. GAJDZIOK. Evaluation of sorptive properties of various carriers and coating materials for liquisolid systems. Acta Poloniae Pharmaceutica - Drug Research. 2015, 72(3): 539-549. ISSN 0001-6837.

Liquisolid systems – evaluation

Evaluation prior to processing into final DF

- Drug solubility
- Flowing properties + Angle of slide
- Porosity, SSA



Evaluation of final LSS

- Pharmacopoieal evaluation according to the final DF type – granulate, capsules, tablets, ODT
- Contact angle, Water uptake – evaluation of LSS wetting
- Dissolution study – drug release evaluation
- Interactions API-EXP (DSC, X-ray diffraction, ssNMR)

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Liquisolid systems – formulations

Optimization of API´s solubility and dissolution profile

- *Famotidine* – dissolution rate increased by 39 % (compared to common tablets)
- *Piroxicam* – significant improvement of dissolution profile (40 % acceleration)
- *Indometacin* - 60% acceleration of dissolution speed

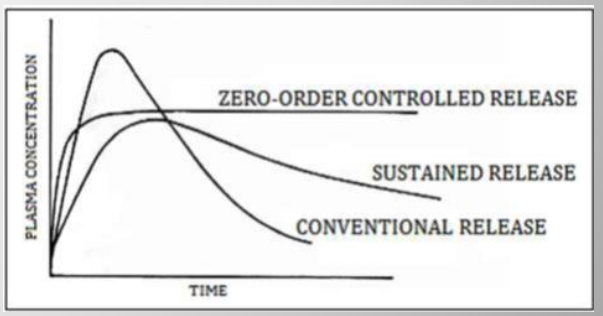
Improvement of pharmaco-kinetic parametres of drugs

- *Hydrochlorothiazide* – bioavailability increased by 15% (compared to common tablets)
- *Atorvastatin calcium* – improvement of *in vivo* pharmaco-kinetic parameters, eg. AUC, t_{max}, c_{max}

Liquisolid systems – formulations

Formulation of tablets with controlled release

- *Propranolol hydrochlorid* - polysorbate 80 - solvent and hydrophobic carrier Eudragit® RL → sustained release profile of drug (0-order kinetics)
- *Tramadol* – confirmed the benefit of HPMC use as an excipient in LSS - controlled release of a drug
- *Theophylline* – proved the positive effect of the use of HPMC to obtain the desired drug release profile



Liquisolid systems – perspectives

- The incorporation of liquid medicines/drugs in liquid form
- Natural extracts, lipophilic substances
- Formulation into a solid form, stabilization
- Cost effectiveness
- Possibility to use common excipients
- Formulation of SEDDS, micro – nano suspensions /emulsions

Liquisolid systems – research

Aim

Optimization of preparation and composition of LSS containing modern hypolipidemic drug - rosuvastatin

- Solvents – PEG 400, PEG 200, PG (7,5% solution; 30-120 % w/w)
- Carrier – Neusilin US2
- Coating material – Aerosil 200

- From tablet evaluation was observed:
  - The amount of liquid strongly influences LSS properties
  - Solvent type influences tablet compressibility – PG is not suitable for LSS with rosuvastatin - ***liquid-squeezing out phenomenon***

Liquisolid systems – research

- Preparation of solution (rosuvastatin in PEG 400)
- Homogenizing with carrier (Neusilin® US2)
  - simple mixing vs spraying
- Addition of coating material (Aerosil 200)
- Mixing with other excipients
  - superdisintegrants and filler (lactose)

- Evaluation of tabletting mixtures
  - pycnometric density, flowability, angle of repose, HR, CI, angle of slide
- Preparing „oblong" tablets (650 mg) using excentric tablet press
  - up to maximum hardness
- Tablet evaluation
  - mass and content uniformity, friability, hardness, height, disintegration time, wettability, dissolution test, stability

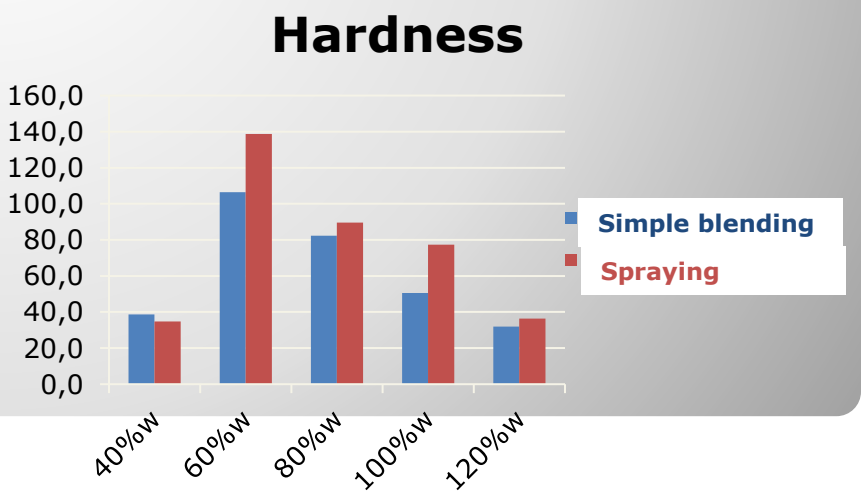
Liquisolid systémy – research

The amount of liquid phase influences:

- Tablet hardness
- Friability
- Height of tablets
- Disintegration time

Preparing using spraying method:

- Improves flowing properties of mixtures
- Increases tablet hardness
- Decreased tablet friability
- Better content uniformity



VRANÍKOVÁ, B., J. GAJDZIOK a D. VETCHÝ. Modern Evaluation of Liquisolid Systems with Varying Amounts of Liquid Phase Prepared Using Two Different Methods. BioMed Research International. 2015, 2015: 1-12. ISSN 2314-6133.

Liquisolid systémy – research

- Based on previous experiments was chosen **best value of L_f and R**
  - L_f = 0.6
  - R = 50

- The influence of **type and amount of superdisintegrant** on tablet properties liquisolid was examined
  - Glycolated-starch sodium salt
  - Cross-carmellose sodium salt
  - Cross-povidone

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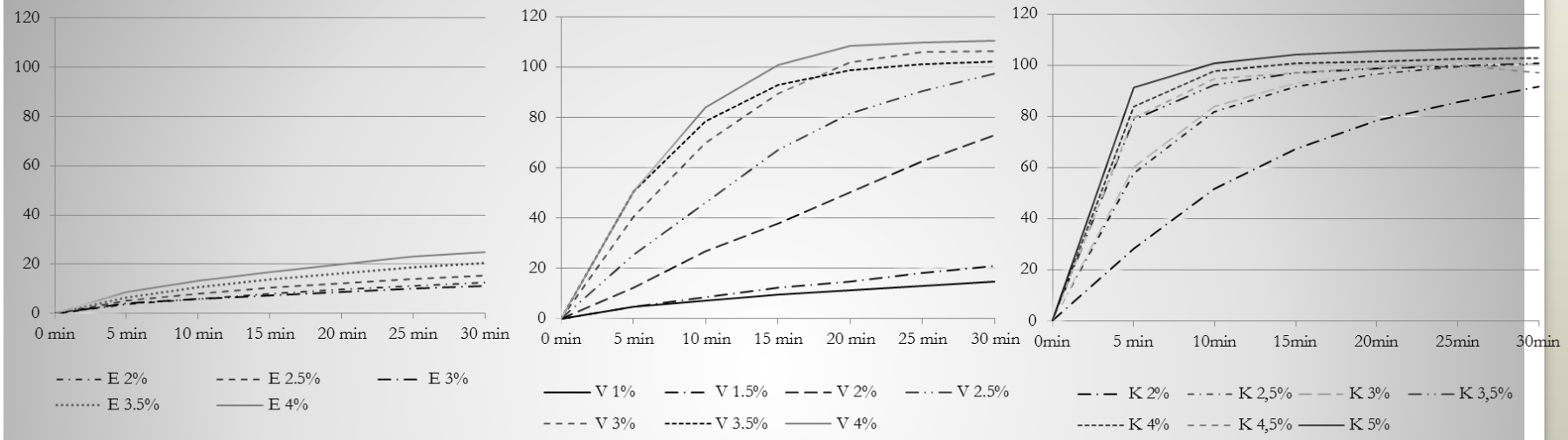
Liquisolid systémy – research summary



- the **best carrier is Neusilin US2** - the highest value of retention potential
- **spraying** using fluid-bed technique leads to improved LSS properties
- optimum **Lf = 0.6**
- Fastest disintegration time and dissolution rate show tablets containing **cross-povidone as disintegrant**

Thank you for attention.