Instructions for exercise

SOLID-LIQUID SYSTEMS

Solid-liquid systems, sometimes referred to by their English name as liquisolid systems (LSS), are modern formulations capable of *increasing the bioavailability of poorly soluble drugs*. Historically, these systems evolved from so-called powder solutions, which were obtained by incorporating a drug solution in a non-volatile solvent into the structure of an inert carrier with a large particle surface area, such as silica. However, it was not possible to transform these preparations into other than powder form, as their properties did not allow them to be compressed into tablets. Despite efforts to modify the compressibility of these systems by adding fillers to improve compressibility (e.g. microcrystalline cellulose), the properties of the formulations were never adapted to the requirements of the pharmaceutical industry. Thus, liquid-in-solid systems are a technological improvement of powder solutions and the main principle of their preparation (Fig. 1) is the absorption of the drug in the liquid phase (solution, suspension, emulsion or self-emulsifying system) onto a highly porous carrier, which is subsequently coated with a very fine material with a high particle surface area (coating material), to form a dry non-adherent powder with properties suitable for further processing (filling into capsules, pressing into tablets, etc.).

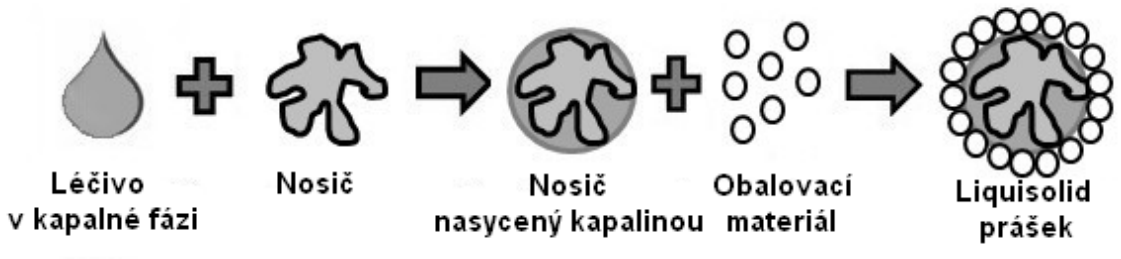

Figure 1: Schematic representation of the preparation of liquisolid powder

Compared to the commonly used incorporation of liquid drugs into a solid dosage form (preparation of gelatin beads), liquisolid systems have a number of advantages, including: simplicity of processing, low production costs, minimization of the effect of pH on drug release rate, improvement of the dissociation profile and increased bioavailability of poorly soluble drug substances, and the possibility of preparing a controlled release dosage form of water-soluble drugs.

Several mechanisms are involved in increasing the bioavailability of drugs formulated into liquisolid systems. The first is the presence of a dispersion of the drug over the entire surface of the carrier, which makes it easier to release the drug from the dosage form. In addition, the wettability of the formulation is enhanced by the presence of a hydrophilic solvent, which is necessary to convert the active ingredient into liquid form, through the disolvation medium. However, the main principle of increasing bioavailability with these systems is the presence of the drug in liquid form, which no longer needs to dissolve after administration to the GIT and is therefore immediately available for absorption into the systemic circulation.

1. Preparation of liquisolid mixture

Prepare a 7,5 % solution of rosuvastatin in macrogol 400 (PEG 400) by homogenisation and grinding in a pearl mill (DYNO-MILL KDL). The resulting dispersion is sprayed onto 110,8 g of Neusilin® US2 carrier (magnesium aluminometasilicate) by injection moulding in a fluidised bed (Glatt). The resulting liquid/powder mixture is sieved through a 1 mm mesh sieve and homogenised in a three-axis homogeniser (Turbula) for 10 minutes. To the mixture is added 2,2 g of Aerosil® 200 (colloidal silica) coating material, sieved (1 mm) and homogenised for 5 minutes. Subsequently, additional excipients are added - 13 g of Vivasol® (croscarmellose sodium) and 132.5 g of Pharmatose® DCL 11 (lactose) filler. The mixture is again sieved (1 mm) and homogenised for 10 minutes.

Table 1: Representation of excipients in the mixture and in the tablets

	PEG 400	**Neusilin® US2**	**Aerosil® 200**	**Vivasol®**	**Pharmatose® DCL 11**
Representation in the mixture [g]	66,5	110,8	2,2	13	132,5
Representation in tablet [mg]	133	221,6	4,4	26	265
% representation	20,5	34	0,7	4	40,8

2. Rating liquisolid mixtures

Pycnometric density:

Determination of the density of solids with a helium pycnometer is a pharmacopoeial test based on the measurement of the volume occupied by a powder of known mass. This volume corresponds to the volume of gas replaced by the powder. In measuring the density by pycnometer, the volume occupied by open pores is not included, but the volume occupied by closed pores or pores inaccessible to the gas is included.

Procedure:The accurately weighed and completely dry test container is filled with a sample of the liquisolid tablet mixture and weighed accurately again. The sample container is placed in the test chamber of the helium pycnometer (Pycnomatic ATC), all necessary data (container ID = 30; weight of empty container and sample container) are filled in on the instrument and the analysis is started.

Saturation:

This pharmacopoeial test determines the ability of the vertical flow (flowing) of crumbled or otherwise treated solids (e.g. powders and granules) under defined conditions. A hopper with a suitable neck angle and diameter, without or with a stem, is used for the evaluation. The hopper shall be kept upright by means of suitable equipment and the whole assembly shall be protected against shocks.

Procedure. The opening is then opened and the time taken for the entire quantity of sample to flow through is measured. The whole test is repeated 3 times.

Spread angle:

The angle of repose characteristically refers to the friction of the powder particles with each other, or to the resistance in the movement of the particles with each other. It is the constant solid angle (relative to the horizontal base) of the cone that is assumed to be formed by the bulking of the sample (Fig. 2). The flow properties as a function of the magnitude of the spreading angle are shown in Table 2.

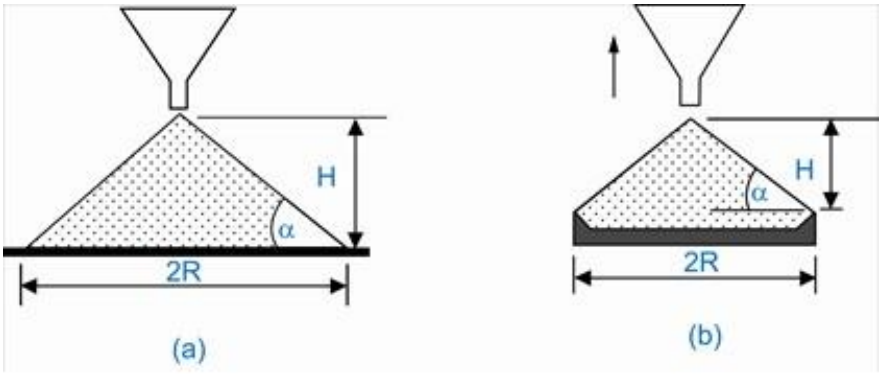

Figure 2: Measuring the spreading angle

Table 2: Flow properties and corresponding spreading angle

Flow property	Spreading angle [°]
Excellent	25-30
Good	31-35
Adequate (no assistance required)	36-40
Average (can be retained)	41-45
Bad (shaking, vibration necessary)	46-55
Very bad	56-65
Very, very bad	>66

Procedure:A funnel 105 mm in diameter, 190 mm high, with a stem 105 mm long and 5 mm internal diameter is used for the measurement, over which 50 g of tablet material is poured freely from a height of 10 cm onto a horizontal support. The height and diameter of the cone are measured with a ruler and the spreading angle is calculated using the formula:

$$tg\alpha = \frac{výška}{0{,}5 \cdot základna}$$

The whole procedure is repeated 3 times.

Bulk and shake densities, Hausner ratio, compressibility index

The bulk density of a powder is the ratio of the mass of the unshaken sample to its volume, including the free volume between the particles. Therefore, the bulk density depends on both the particle density of the powder and the spatial arrangement of the particles. It is expressed in grams per millilitre because graduated cylinders are used for measurement. In addition to the graduated cylinder measurement, which is most commonly used, volumetric measurements or measurements in a measuring vessel can also be used.

Shaken density is the increased bulk density achieved by mechanical vaulting of the container containing the powder sample. After recording the initial volume and weight of the powder, the graduated cylinder or container is mechanically vaulted and the volume is read off until further small changes in volume are observed. Mechanical vaulting is achieved by lifting and then dropping the cylinder or container.

Because the interactions between particles affect the flow properties of the powder, a comparison of bulk and shake densities can be relatively important in determining the degree of interaction for a given powder. This comparison is often used as a compressibility index or Hausner ratio. The compressibility index and Hausner ratio measure the ability of a powder to be compressed. These measurements are a measure of the ability of the powder to settle and allow an estimate of the relative importance of the interactions between the particles. For free-flowing powders, these interactions are less significant and the values of bulk and shake densities are close together. For poorer flowing material, where interactions between particles are often increased, a larger difference in bulk and shake densities are observed. These differences are also reflected in the compressibility index and Hausner ratio values (Table 3).

Table 3: Powder flow pattern and corresponding compressibility index and Hausner ratio values

Sweetenability index [%]	Nature of the flow	The Hausner Affair
1-10	Excellent	1,00 - 1,11
11 - 15	Good	1,12 - 1,18
16 - 20	Reasonable	1,19 - 1,25
21 - 25	Average	1,26 - 1,34
26 - 31	Bad	1,35 - 1,45
32 - 37	Very bad	1,46 - 1,59
>38	Very, very bad	>1,60

Procedure:30 g of tablet material is poured freely into a dry graduated cylinder (100 ml) without squeezing. The graduated cylinder is fixed in the holder and the bulk volume V_0 is read. Then make 10, 500 and 1250 shakes and read off the corresponding shake volumes V_{10} , V_{500} and V_{1250} . From the values obtained, the bulk and shake densities, the Hausner ratio and the compressibility index are calculated:

$$\rho = \frac{m}{V}$$

$$Hausnerův\ poměr = \frac{V_0}{V_{1250}}$$

$$index\ stlačitelnosti = 100 \cdot \frac{V_0 - V_{1250}}{V_0}$$

Slip angle:

The slip angle is a specific parameter used to determine the flow properties of powdered excipients and liquisolid mixtures. Slip angle assessment is the preferred method for determining the flow properties of powders with particles smaller than 150 µm. The actual test procedure consists of placing a carrier sample on one end of a smooth metal plate, which is gradually lifted (Fig. 3). The angle at which the powder begins to slide is recorded. This angle is referred to as the slip angle, with a value of 33° indicating that the powder has optimum flow properties for the preparation of liquisolid systems.

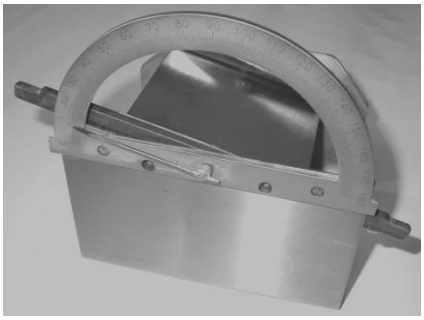

Figure 3: Slip angle measuring device

Procedure. One of the ends of the plate is raised upwards until it reaches a level at which the powder slides down. At this position, the slip angle value is read. The measurement is taken 3 times.

3. <u>Tablet moulding</u>

The prepared tabletting mixture is pressed on an eccentric tablet press to form oblong tablets (18 x 8 mm) of constant weight 650 mg using maximum pressure.

4. <u>Rating of liquisolid tablets</u>

Pycnometric density:

Thanks to the values of pycnometric density of the tablets and the tablets themselves, it is possible to calculate the intraparticular porosity of the resulting liquisolid tablets.

$$intrapartikulární\ pórovitost = \left(1 - \frac{\rho_{tablet}}{\rho_{tabletovin}}\right) \cdot 100$$

Procedure:The accurately weighed and completely dry test container is filled with liquisolid tablets and weighed accurately again. The sample container is placed in the test chamber of the helium pycnometer, all necessary data (container ID = 30; weight of empty container and sample container) are filled in on the instrument and the analysis is started.

Mass uniformity:

During the determination of mass uniformity, the weight of each tablet is determined. From the values obtained, it is determined whether all tablets conform to the tolerance allowed by the pharmacopoeia (Table 4). Out of 20 randomly selected samples, no more than two units may differ from the permitted deviation and no value may differ by more than twice this deviation.

Table 4: Tolerances for individual tablet weights

Average tablet weight [mg]	Variation of individual masses [%]
80 or less	10,0
More than 80 and less than 250	7,5
250 and more	5,0

Procedure: 20 randomly selected tablets are individually weighed on an analytical balance. From the values obtained, it shall be determined whether the tablets conform to the maximum permitted deviation of 5 % from the average weight laid down in the pharmacopoeia in force.

Fortress:

The essence of the test is to evaluate the resistance of tablets to crushing under defined conditions. The force required to crush the tablet is determined. The strength measuring apparatus consists of two opposing jaws, one of which moves towards the other. The surface of the jaws shall be smooth, flat and perpendicular to the direction of movement and shall not be less than the contact area of the jaws with the tablet.

Procedure:Twenty randomly selected tablets are measured for strength using a strength measuring device. Each of the tablets is placed between the jaws of the instrument (10 tablets longitudinally, 10 tablets transversely), which move against each other. After each measurement, tablet residue and fine dust is thoroughly removed with a brush.

Tablet abrasion*:*

The test is used to determine the resistance of tablets subjected to mechanical stresses (such as mutual abrasion, drops and impacts), which may lead to disruption of the surface continuity, breakage or splitting. A rotating drum made of plastic, which does not generate static electricity, is used for the determination. The internal baffle of the drum floats the individual tablets, which then fall against the wall or bump into each other. A satisfactory

result is considered to be a weight loss of less than 1,0 % and a condition where no tablet is broken, fractured or has major chipping.

Procedure:Approximately 6.5 g of tablets (equivalent to 10 tablets) are thoroughly dusted and accurately weighed (analytical balance). The tablets are placed in the plastic drum of the abrasion apparatus. The instrument is set to a speed of 25 revolutions per minute, 100 revolutions for a total of 4 minutes, and the measurement is started. When the drum has finished rotating, the tablets are dusted again and accurately weighed. The percentage weight loss (tablet abrasion) is calculated from the weight differences.

Fracture test:

The disintegration test determines whether the tablet disintegrates in a liquid medium in a prescribed time. Tablets are considered to be completely disintegrated if no residue of the tablet under test remains, except for a soft residue with no visible solid core. The apparatus used for the measurements consists of a 6-cup suspension device (Figure 4), a beaker containing the selected medium, a thermostatic unit heating the medium to a temperature of 35 °C-39 °C and a device which allows vertical movement of the cups in the medium.

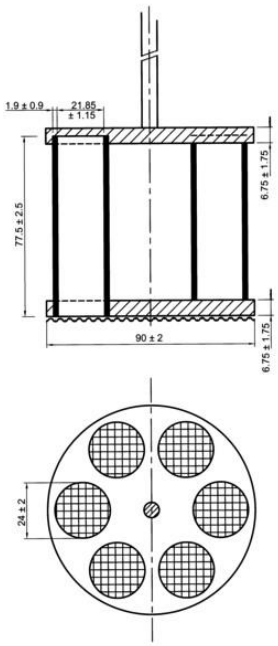

Figure 4: Basket for tablet disintegration test

Procedure:One tablet is placed in each of the six cups and the entire system is placed in a beaker of distilled water at 37 ± 1 °C. After switching on the apparatus, the cups are moved vertically in the beaker of medium and the time at which each tablet has completely disintegrated is recorded.

Absorption:

Soakability evaluation is one of the specific tests used to evaluate final solid-liquid systems. This test is used to determine the wetting rate of the final tablet, which is closely related to the rate of disintegration or release of the drug from the final liquisolid system.

Procedure:Place a sponge (5 x 5 cm) in a petri dish with 10 g of aqueous dye solution. The accurately weighed tablet (m_0) is then placed on the sponge. Record the time at which the top surface of the tablet is wetted and when the tablet is completely wetted. The tablet is then weighed again (m_1) and the absorbance calculated:

$$nasákavost = 100 \cdot \frac{(m_1 - m_0)}{m_0}$$

Fluidní zařízení Uniglatt

návod k použití

Příprava přístroje:

- Z přístroje sejměte vrchní část pracovní komory.
- Pod ventilátor připevněte filtry (s ohledem na používaný materiál).
- Připevněte zpět vrchní část pracovní komory.
- V případě použití horního nástřiku připevněte trysku do otvoru ve vrchní části pracovní komory.
- Připevněte trysku k přívodu tlakového vzduchu (zezadu přístroje). (V případě použití spodního nástřiku se tryska připojuje až po vsunutí spodní části pracovní komory)
- Zapojte peristaltickou pumpu do zástrčky zezadu přístroje.
- Vložte spodní část pracovní komory pod vrchní část a otočte tlačítkem "Pneumatic Heben-senken" na dolním panelu.

!! PŘED UVEDENÍM PŘÍSTROJE DO CHODU SE UJISTĚTE, ŽE JE ZAPNUTÁ DIGESTOŘ A ZDA JE PŘÍSTR
PŘIPOJEN KE ZDROJI TLAKOVÉHO VZDUCHU!!

Uvedení přístroje do chodu:

- Na horním ovládacím panelu zmáčkněte černé tlačítko „Turbine".
- Pomocí páčky „Zuluftklappe" na dolním panelu upravte množství přiváděného vzduchu, s pomo regulátoru otáček „Mindestdrehzahl" upravte výkon motoru.
- Nastavte teplotu vzduchu pomocí tlačítka „Zulufttemperature" na horním panelu.
- Upravte množství vzduchu přiváděného do trysky pomocí otočného tlačítka „Sprühluft" (dolní panel). Pro automatický nástřik otočte levým tlačítkem „Doslerpumpe" na horním panelu, pro ruční nástřik držte zmáčknuté pravé tlačítko „Doslerpumpe".
- Dle potřeby zmáčkněte tlačítko „Rütteln" (dolní panel) pro oklep filtrů.
- Před vypnutím přístroje ukončete automatický nástřik otočením tlačítka „Doslerpumpe" do původní polohy a zastavte přívod vzduchu do trysky otočením tlačítka „Sprühluft".
- Přístroj se vypne stlačením červeného tlačítka „Turbine" na horním panelu.

UNIGLATT AG