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Diploma thesis

A study of the influence of lubricants on the ejection force of the tablets

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Porto & Hradec Králové 2015 Nikola Novotná

Author's Statement

I declare that this thesis is my original copyrighted work. All literature and other resources I used while processing are listed in the bibliography and properly cited. This work has not been used to achieve same or another degree.

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In Hradec Králové …… Nikola Novotná

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1 Abstract, Abstrakt

Abstract

The aim of this study was to evaluate the effect of the type of lubricant, its concentration and mixing time with granules on the tablet hardness, ejection force and the lubrication index. Lactose was used as a filler in granules and polyvinylpyrolidone as a binder. Granules were prepared by wet granulation. Three types of talc were used in concentrations 1%, 3%, 5%, 7% a 10% and magnesium stearate in concetrations 1%, 2% a 3% as lubricants. Tablets were produced by tablet press DOTT Bonapace (model CPR-6) with the possibility to measure the force of the upper and lower punch and force-displacement. These values were used for the calculation of the lubrication index. The values of lubrication index were used for the lubricants comparison.

The lubrication index with magnesium stearate did not change either with increasing concentration or with mixing time with granules. In case of each type of talc, the lubrication effect rose with increasing concentration but time of the mixing did not have any significant effect on the lubrication potential. Tablet strength decreased with higher lubricant concentration and longer mixing time when magnesium stearate was used. With increasing concentration of the lubricant tablet strength with talc first increased then stagnated or started to decrease. The higher mixing time increased the hardness of the tablets containing talc. Results show that the magnesium stearate is a better lubricant than talc even in low concentrations. Values of lubrication index reach 0.98. In case of talc, it is necessary to use higher concentrations to reach sufficient values of the lubrication index. The maximum values for talc reach 0.93 in 10% Microtalc 8 and Mictotalc 30.

Abstrakt

V diplomové práci byl hodnocen vliv typu mazadla, jeho koncentrace a doby mísení s granulátem na pevnost tablet, ejekční sílu a lubrikační index. Plnivem v granulátu byla laktosa a pojivem polyvinylpyrrolidon. Granulát byl připraven metodou vlhké granulace. Jako mazadla byly použity tři typy mastku v koncentracích 1%, 3%, 5%, 7% a 10% a stearan hořečnatý v koncentracích 1%, 2% a 3%. Doby mísení byly pro mastek 5, 10, 15 a 20 minut a pro stearan hořečnatý 10 a 20 minut. Tablety byly vyráběny na tabletovacím lisu DOTT Bonapace (model CPR-6) s možností měření sil horního a dolního lisovacího trnu. Tyto hodnoty byly použity pro výpočet lubrikačního indexu. Mazadla byla porovnávána pomocí lubrikačního indexu.

Lubrikační index u stearanu hořečnatého se neměnil se zvyšující se koncentrací ani s dobou mísení s granulátem. U všech typů mastku se lubrikační efekt zlepšoval se zvyšující se koncentrací, doba mísení neměla výrazný vliv. Pevnost tablet se stearanem hořečnatým se snižovala se zvyšováním jeho koncentrace a rostoucí dobou mísení. Pevnost tablet se se zvyšujícím se obsahem mastku zvyšovala do určité koncentrace, pak stagnovala, nebo se začala snižovat. Rostoucí doba mísení zvyšovala pevnost tablet. Výsledky ukázaly, že stearan hořečnatý je účinnější mazadlo již v nízkých koncentracích, hodnoty jeho lubrikačního indexu dosahují 0,98. V případě mastku je nutné použití vyšší koncentrace. Nejvyšší hodnoty jeho lubrikačního indexu dosáhly 0,93 a to u koncentrace 10% u typu Microtalc 8 a Microtalc 30.

2 Aim of the study

The objective of this work was to study the compressed ejection force, tablet strength and lubrication index of granules with added lubricants. The affecting factors which were measured are concentration of the lubricants, particle size and the mixing time. Lactose was used as a filler and polyvinylpyrolidone as a binder. Granules were made by wet granulation. The effect of the following two lubricants were evaluated - Microtalcs with different size of grains and magnesium stearate. Lubrication index of these powders was calculated based on the upper and lower punch force values from tablet press.

3 Introduction

Tablets are one of the most common dosage forms. They are pressed from powders or granules with pharmaceutical excipients, which positively affect properties of the mixtures. When the tablets are manufactured, it is necessary to release them from their dies completely. Lubricants reduce the friction during tablet compression and increase the free flow of powders. They also tend to equalize the pressure distribution in a compressed tablet. Pharmaceutical excipients called anti-adherent belong to a group of lubricants also preventing adhesion and facilitating the tableting process. Friction reduction is achieved by interposing a film of lubricant between two sliding surfaces. Particles of the lubricants move to fill pores in granules and give a less porous aggregate. For assessing lubricity, the lubrication index, also called R value, is used. In this work, the lubrication index was used to evaluate the results. Lubricants are usually added at the very last step before compression. Only after that, the presence of the particles can be provided on the surfaces of the granules and also in between the particles and parts of the tableting machine. The closer the lubrication index to value of one, the better the achieved effect. Tablet lubricants mostly used in production are magnesium stearate, zinc stearate, aluminium stearate, talc, starch and others. [1]

4 Theoretical part

4.1 Tablets and their preparation

Tablets are the most common solid dosage form. They provide reproducible medication and patient freedom. Tablets are a carrier for the active ingredients and they have to get volume, since the amount of active ingredients is very little. Variety of the pharmaceutical excipients are added into the tablets to fill the volume, to held ingredients together, to help with the dissolution or mask the taste. The tablets offer several advantages: precision of dosage, stability of chemical and physical activity of the drugs, durability of physical characteristics for prolonged periods of storage and convenience of administration.[2], [3]

Tablets contain mixture of one or more active ingredients with pharmaceutical excipients such as diluents, binders, lubricants, disintegrants and others. These modified the behaviour of dosage forms. But excipients should not have a negative effect on the stability, safety and efficacy of active compounds. Tablets are mostly intended for oral administration. There are many types of tablets such as: coated, uncoated, chewable, effervescent, and dispersible and more others.[4], [5] Tablets can be characterized by weight variation, content uniformity, hardness, thickness, friability disintegration and dissolution. These factors have to be controlled during tablet production, to ensure the quality standards.[6]

Methods of the tablets preparation

There are three basic techniques used for preparing powders for a tablet compression. They are wet granulation, dry granulation and direct compression. These techniques are chosen individually as required, and according to the features of the powder. The granulation process is used more often, as the size enlargement is preferable, thanks to its advantages, which are specified below.[7]

Granulation is the pharmaceutical process, when powder materials are converted into aggregates called granules, which are then compressed into the tablets. The process of granulation has several advantages in the tablet manufacturing process of a tablet: good flow, good compatibility, prevent segregation, uniform distribution of drug, controllable drug release, improved compression characteristics and reduced dust.[7], [8]

Good granulates should contain spherical shape particles or similar. Sphere shape minimizes interparticulate friction and it is almost without static charge. For a good granulation it is also important to present a range of particle sizes: small percentage of fine and coarse particles and the range particles between. Fine particles fill space between the large ones and this improves the fill of the die and also provides physical bonds between the larger particles.[2]

Granulation methods can be divided into two types; wet methods and dry methods. Wet methods use a liquid during the process.[9]

Wet granulation

The wet granulation is a process of size enlargement and we can see the whole method in Figure 1. The first stage of wetting granulation is dry mixing of components. The result of this process should be a homogenous blend. The next step is granulation. The liquid is added to mixed solids and mainly a shear granulator is used as a granulating apparatus. Drying follows after granulation. The liquid (usually water) is removed by evaporation. Tablet granules are most frequently dried in the fluid bed drier, where the hot air comes from below over the solid. The moisture content within granules is reduced to an optimum concentration. Mass is after drying quite coherent and it needs to be broken up, therefore, the next step is sieving. For the break of the aggregates and to obtain relatively uniformly sized granules, the dried material is passed through a sieve. Granules with narrows particle size distribution eliminate segregation.[3], [7]

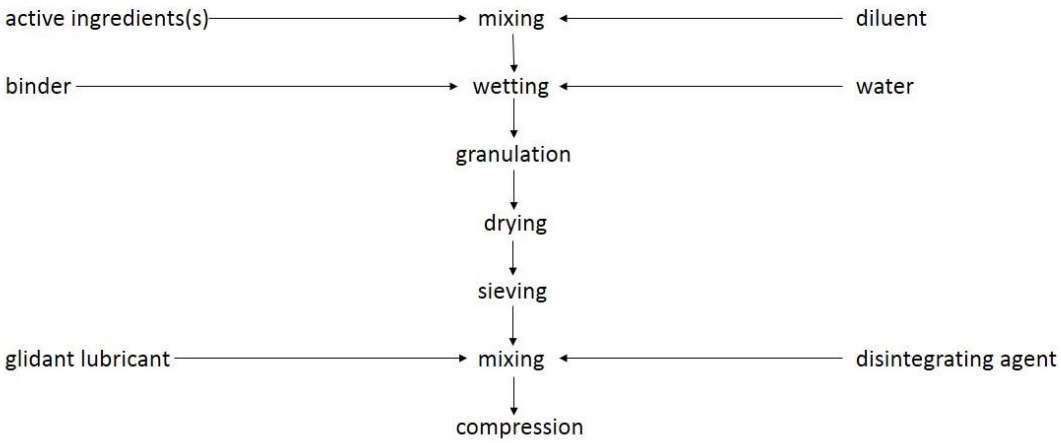

Fig. 1 Process of the wet granulation in tablet manufacture [7]

Dry granulation

This method is used when the drugs are sensitive to the moisture or when drugs do not compress well after wet granulation. The water, which is the usual granulating liquid, can cause hydrolysis of tablet ingredients. Furthermore, in wet granulation heat is used to remove the liquid. It can affect stability of the ingredients and can cause another unacceptable reactions.[7]

There are two methods of dry granulation. The first one consists basically of producing conventional tablets called "slugg", using heavy-duty tableting press. The second method uses a roller compactor to squeeze powder between two rollers, producing a sheet of material. In both methods it is necessary to mill the intermediate products. The products are broken down by a milling technique for granular material, which is sieved for separating the desired size fraction. The procedure of dry granulation is shown in Figure 2.[9]

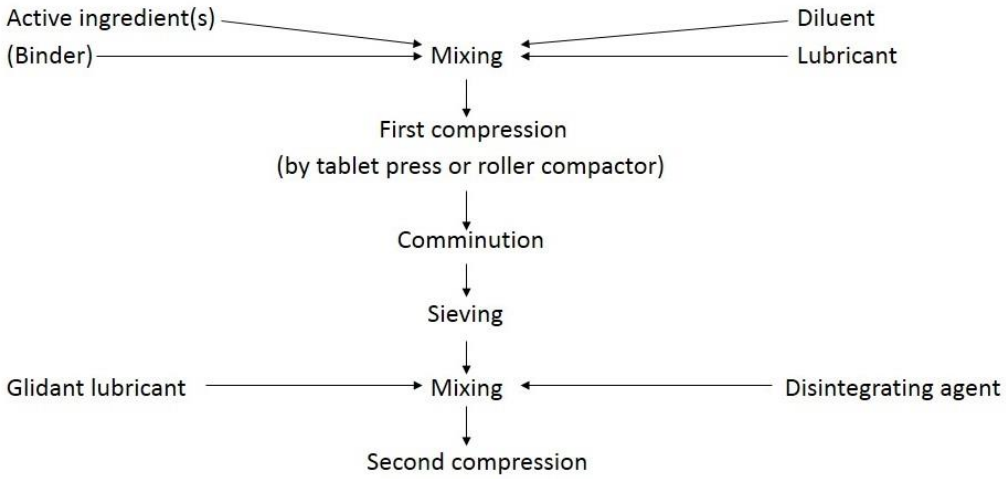

Fig. 2 Process of the dry granulation in tablet manufacture [7]

Direct compression

Compressing uniform volumes of powders is the simplest and the fastest way of forming a tablet without granulation. The process of the direct compression is shown in Figure 3 *(see below).* Direct compression is more economic, because it saves energy and less steps to prepare tablets are needed. There are many factors in tablet design, which should be considered, such as the physicochemical properties of components and tableting machines. In direct compression, the components can behave as individual particles, as they are not stick together. Thanks to this and the wide particle size distribution, the significant segregation can happen easily. Direct compression requires the use of pharmaceutical excipients with strictly defined properties, because the powder materials have to demonstrate good compressibility and flow ability for a successful compression.[7]

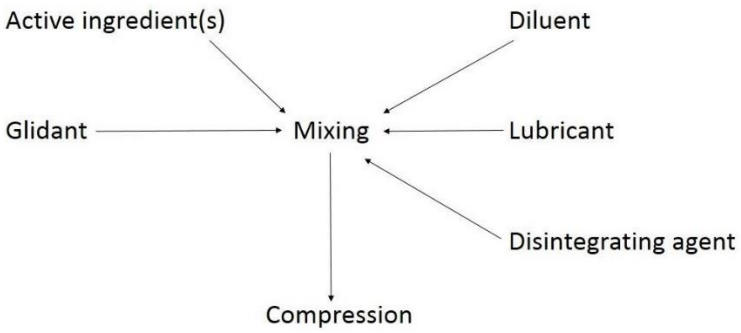

Fig. 3 Process of the direct compression in tablet manufacture [7]

4.2 Tableting process

The powder mixture is dosed by a hopper (or feed frame) during the manufacturing process into the die. The position of the lower punch defines the volume of the subsequent tablet mass. The tablet is ejected by the lower punch. The position of the upper punch gives the compression force, which defines its immersion depth into the die and the reagent force that is built up during the densification of the material. The pressure at the upper punch is normally higher than the pressure at the lower punch. The reason is that part of the pressure is lost in the material and the force against the die wall during the compression.[9], [10]

Tableting cycle is divided into three stages[9], [10]:

1. Filling – the volume of the granules/powders is measured
   The filling volume is determined by the diameter of the die hole and the depth (height of the die cavity). The die is filled by the hopper, which is moved back and forth over the die and when the lower punch goes down.
2. Compression – granules are formed into a solid by pressure
   One of the possibilities of compression is that the lower punch is stable and the upper punch moves down for compression. In this case the surface hardness of the tablets in not the same on the upper and lower sides. Another possibility is that both of punches are moving to each other and compress the powder from both sides. The process after the compression is called decompression. In this process

the tablet relaxes, when the punches leave each other. Afterward the process is called elastic recovery.

3. Ejection – a new tablet is ejected and the next will be formed.

Tableting machines

There are two types of tableting machines, the eccentric and rotary tableting machines. The newest rotary tableting machines fill the dies by centrifugal force. Another innovation is a special machine which operates by ultrasound.[7]

The tablet compress machine consists of [2]:

- Hopper – stores materials for compressing
- Feed frame – putts the materials into the dies
- Die – controls the shape and size of the tablet
- Punches – compress the materials

Single-punch tableting machines

Eccentric tableting machines are good choice, when you want to use the single-punch tableting machine. They are used mostly for research. There is one pair of punches. The upper punch is mobile while the lower is fixed during the compression. The lower punch moves up only to eject the tablet and moves down, when the die is filled by granules. The movement of the upper punch into the die is determined by operation conditions. The compression forces are extended after the contact with the granules in the die. These tablets have a different hardness on the upper and lower surfaces. The compression and ejection forces may be monitored by transmitting signals received from strain gauges, bonded to the upper and the lower punches, with a radio link.[10], [11]

Rotary tableting machines

Rotary tableting machines work with several punches and die sets which move in a circle. These machines are commonly used for the tablet production. The die table, where the dies are fixed in a round, moves with the lower and upper punches on tracks. The hardness of these tablets is the same on the upper and lower surfaces, because the force from the compression wheels in the densification process is evolving equally to both punches.[10]

4.2.1 Pharmaceutical excipients in tablets

Besides the active ingredients, the tablets contain other substances with specific functions known as excipients. Pharmaceutical excipients can be called additives or inactive ingredients. Pharmaceutical excipients may vary solubility, stability, metabolism and processability. They change the physiochemical and biological parameters of drugs and also change the properties and the formulation during the manufacturing processes. Almost all tablets require the addition of excipients to produce a satisfactory drug release, to achieve acceptable physical and mechanical properties, to facilitate their manufacture and create pharmaceutical dosage forms suitable for the administration to patients. Many factors must be considered before we select the pharmaceutical excipient: compatibility with the drug, good stability, no toxicological effect and ease of accessibility and distribution. The amount and type of excipient should be considered to determine the size of the dosage form. Almost every excipients have more functions and many uses.[6], [12]

There are five major excipient categories: diluents, binders, lubricants, glidants, disintegrants. The groups are categorized according to the excipient main function.[6]

Fillers (Diluents)

Diluent is a substance used as filler, which increases the bulk of the formulation. The diluent is necessary when we need a supplement tablet size, usually when we have a small amount of drug. Good fillers have a good compatibility and flow properties, acceptable taste and if possible chemically inert.[6], [13]

Examples: lactose, microcrystalline cellulose and dibasic calcium phosphate dihydrate.[6]

Lactose has white or almost white crystalline particles or powder, freely but slowly soluble in water, practically insoluble in alcohol. It is a disaccharide derived from glucose and galactose got from milk. Lactose is used as a filler in tablets, because lactose improves compressibility. Lactose is quite stable and does not react with most medicinal substances. Various lactose grades have different physical properties such as particle size distribution and flow characteristics. For wet-granulation are usually used fine grades of lactose, because they permits better mixing with other formulation ingredients and utilizes.[14]

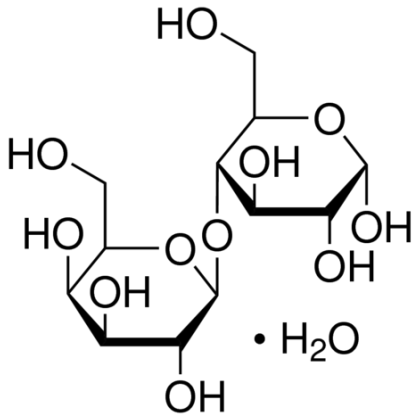

Fig. 4 D (+) lactose monohydrate [15]

Binders (Granulating agents)

These substances are used to improve adhesion of powder particles in tablet granulation. They also increase granule strength. Binders have to form a hydrophilic film on the particle surface for theirs effectiveness. Therefore binders may vary the disintegration and dissolution (adding too high concentration of binders will retard the dissolution, because the film can form viscous gel on the granule surface). Also too much binders can make hard granules, which need a higher pressure to compact into tablets.[6]

Examples: Polyvinylpyrrolidone (PVP, povidone), starch, gelatine.

Polyvinylpyrrolidone is widely used as an excipient especially in tablets. PVP is used in concentrations 0.5-5% as a binder, but it can be also used as a suspending, stabilizing or increasing viscosity agent. There are many types of povidone and they are characterised by their viscosity in solution. PVP is a fine, odourless and white colored, hygroscopic powder.[16]

Glidants

Glidants improve flow characteristics of the granules. Glidants are good for the uniformity of tablet weights, because it depends directly on how uniformly the die cavity is filled. It is added to avoid of powder cohesiveness. The effects of a glidant on the flowability depend on several factors: chemical and physical affinity for the powder, concentration of the glidant, mixing time, moisture content and smaller average of particle size and shape against to those of the powder. The mechanism of the glidant action is described by few rules. Glidants should be distributed in the host particles (coat them completely and smooth irregularities in their shape), minimized friction by adsorption of

the glidant particles to the granulation surfaces and reduced van der Waals interaction by physical separation of particles. For a good effect of the glidants it is important to have much smaller particles than those of the host powder. When the glidant is added in a big amount, the powder flowability may be decreased.[13], [17]

Examples: colloidal silicon dioxide, corn starch.[13]

Disintegrants

Pharmaceutical excipients named disintegrants are added into the tablets to promote rapid breakup to increase the surface area and aid the drug dissolution, when the tablets are in contact with a fluid environment. They are important for immediate release of the active compounds from compressed mass. They can be acted by two different mechanisms such as swelling or capillary action.[18]

Examples: starch 1500, explotab, sodium carboxymethyl cellulose.[13]

4.2.2 Lubricants

Lubricants usually form a film/layer between the surfaces or at interfaces to decrease the friction. The penetration of the lubricants into the surface asperities is important for its efficiency.[19], [20] Long chain molecules with active end-groups like stearic acid and its metallic salts are necessary for the boundary lubrication. These end-groups form layer, which prevent a friction between the powder particles and the surfaces. The lubricants also reduce the shear stress, which is required for pushing a tablet out of a die. Due to improve flowability and reduction of wall friction by lubricants, the compression pressure and mechanical properties of compacts (density) are also changed. There are few factors that should be considered for selecting an appropriate lubricant for solid dosage forms: chemical compatibility with drugs, minimum negative effects on the performance of the final dosage forms, non-toxic and being able to form a resistant layer covering surfaces. Other important factors are the optimal concentration and the mixing time of blends. If the lubricant concentration and mixing time are low or inadequate, the sticking and binding in the die cavity can happen. High concentration of lubricant or over mixing time often affects the product by reduction of tablet hardness, longer disintegration, compression variability and lower rate of dissolution. The lubrication is usually added at the end of the granulation process in the outer phase, when other components have been mixed already. They are added before the compression, because the lubricants have to

be on the surfaces of the granules and in between them and the parts of the tablet press.[2], [21] The effect of the lubricant on bonding properties depends on the completeness of the film, which is formed during the mixing process. The completeness of the film is affected by the velocity of the film formation and the possibilities during the compaction and consolidation. These two factors of film formation are influenced by [22]:

- Nature and properties of the lubricant and the host particles
- Presence of other pharmaceutical excipients
- Mixing time
- Type, size and content of the mixer
- Specific surface area of the particles

The forming of the lubricant film depends not only on the compaction and consolidation behaviour of the lubricant but also on the compaction and consolidation behaviour of the host particles and storage conditions of lubricated products. One of the conditions for sufficient forming of film is the distribution of lubricant particles among the host particles. In other words, the velocity of forming the lubricant film depends on the particle size and flow qualities of the host particles. Lubricants with large surface area like magnesium stearate have five times higher reduction in tensile strength than talc.[22]

Examples: magnesium stearate, talc, fumaric acid, calcium stearate.[7]

4.2.2.1 Magnesium stearate

Magnesium stearate (MS) is a main lubricant used in the pharmacy industry for the tablet manufacture at concentrations between 0.25% and 5.0%. It is a white, fine and solid powder at room temperature, greasy to the touch and practically insoluble in water and in ethanol. It is used as a flow agent too. MS can be derived from plants, animal sources or by chemical reaction. Magnesium stearate is a mixture of different fatty acids composed mainly of stearic acid and palmitic acid with a few other fatty acids. Structure of MS is shown below in the Figure 5. Magnesium stearate can form different hydrates upon exposure to humidity. Commercial supplies usually contain a mixture of various hydrates in unknown ratios and the most efficient lubricant of all is dehydrate. Amount of water of hydration in the lubricant effect tendency of over lubrication. Smaller particle size and the increasing surface of magnesium stearate improve its lubrication efficiency, because the increase of surface area can provide more surface coverage. The particle-particle bonding is weakened with a higher coverage of particle surfaces by MS, so even

the tablets are weakened. Magnesium stearate is a hydrophobic lubricant so the dissolution is slower and it cannot be used e.g., in effervescent tablets.[14], [21]

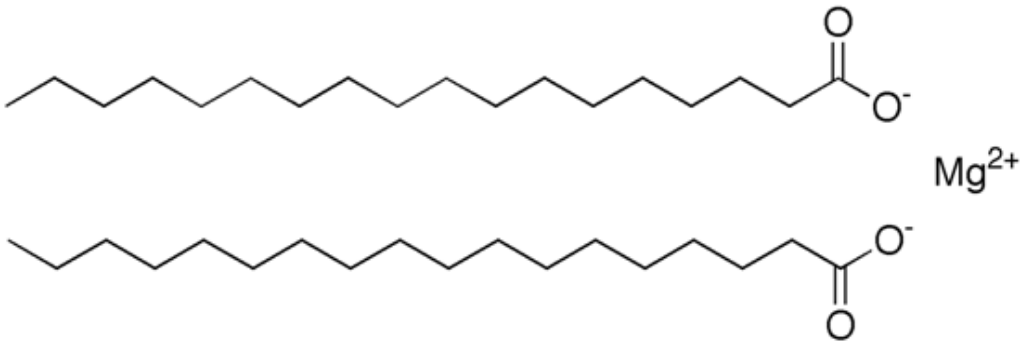

Fig. 5 Structural formula of the magnesium stearate [23]

4.2.2.2 Talc

Talc is selected, powdered and hydrated magnesium silicate. It is a white or almost white, very fine, unctuous and crystalline powder free from grittiness. Talc is practically insoluble in water. It is used as a lubricant, glidant or dissolution retardant.[14]

Talc is a hydrophobic lubricant with weakly-bonded sheet structure which gives essential lubricity for pharmaceutical operations and regulates the flow. The chemical structure is [Mg_3 Si_4 O_{10} $(OH)_2$]. Talc is selected and pulverized native hydrous magnesium silicate. The powder of talc may contain small quantities of other minerals. The method of preparation can change the antisticking power of talc. It has a crystalline structure with a lamellar shape. Talc is mostly less efficient in lubrication than the magnesium stearate but it can be used as a replacement of MS. Talc improves the tablet hardness, the appearance and friability in pharmaceutical formulations.[24]

4.2.2.3 Lubrication index and influence of the lubricants on the tablet strength

Lubrication index (R –value)

The R – value expresses the ratio between the maximum force of the lower punch and maximum force of the upper punch. R – value is usually called lubrication index and it is used to compare the lubricants. The maximum value of the lubrication index is 1. The lubrication ability increases with the increasing value. Another way how to evaluate the effectiveness of lubricants is the ejection force.[7]

Hardness

The hardness is evaluated as a tablet strength. It is defined as the force needed to break a tablet in a diametric compression test. The tablet is placed between two anvils and the crushing force required to break the tablet is recorded. So the hardness is tablet´s crushing strength. The greater the pressure applied, the harder the tablets, but also the manufacturing process and the composition may change the tablet´s hardness. The tablet should be so hard to resist usual manipulating or transportation but they should not have a problem in dissolving or disintegrating after swallowing. The hardness is a function of the die fill and compression force. The tablet hardness can be affected by amount and mixing time of lubricants and excipients. [6] The lubricant forms an adsorbed film around individual granules after adding as a powder to granules. This coat acts as a physical barrier for the bonding. It has been seen in numbers of studies that with an increase in mixing time with lubricant, the tablet strength decreases. This effect strongly depends on the material used and a number of other factors. These factors include the nature and properties of the lubricant and other tablet ingredients, and methods of production. The decrease of the tablet strength is caused by the formation of the film, which interferes with the binding of the particles in granulate. Before compression, the bonds between excipient-excipient are strong, but phenomenon of decreased hardness of tablet after prolonged mixing time which is attributed to weaker bonds after compression between lubricant-lubricant.[22]

Most of the drugs and excipients used in the tablet formulation are in solid state as amorphous powder or crystals. There are differences in particle size, surface area, wetting, crystal morphology, flow properties, compressibility and many physical properties of drug, excipient and their blends. All of these properties can influence the hardness of tablets or the lubrication index of granules in tablet press. It is necessary to understand and characterize these properties in pharmaceutical preformulation testing. The characterization of powders is essential to quality control.[6]

4.2.2.4 Lubricants in literature

S. Patel et al. [25] studied lubrication potential of two samples of magnesium stearate (MS) on instrumented rotary tablet press. MS was blended with dicalcium phosphate dihydrate (DCP) and microcrystalline cellulose (MCC). This blend containing 92% DCP, 8% MCC and 0.2% of MS was mixed in different mixing times (10, 20 and

30 minutes) and tableting speed (10.7, 13.8, and 17.5 rpm). The compression force was kept constant at 13.8 ± 0.2kN as well as the weight of the tablets 300 ± 4 mg. The temperature was 25 ± 5°C and the relative humidity around 40 ± 4%. The aim of the study was to identify the relationship between the lubrication potential and the solid-state properties of MS during a real tableting condition. The results for longer mixing times were lower ejection forces. The mixing time has an influence on the surface distribution of the particles of MS, which affects the frictional forces. The results from this study show that a longer mixing time gives a greater surface distribution. With the increasing mixing time, the friction force decreases. The results show differences in forces and lubrication efficacy between two samples of MS from different manufacturers. It is caused by the diversity in particle size, solid-state properties, specific surface area and d-spacing of these samples.

N. Faqih et al. [26] studied the influence of the moisture and formulation composition on the flow properties of cohesive powders. The moisture and concentration of MS has an effect on the formulation, compaction, hardness, friability, porosity and chemical stability. These few substances were used: fast-flo lactose, Avicel 102, Avicel 101 and regular lactose. Final blend was mixed with different levels of lubricant (0.25%, 0.5%, 1.0% and 2.0%) and the flow properties were measured at different levels of relative humidity (20%, 30%, 40% and 50%). In the case of lactose, the cohesion was increased as the moisture increases and condenses on the surface and that is why the flowability decreased. But the cellulose shows opposite effect. The flow characteristics were measured by the gravitational displacement rheometer (GDR). An experiment was made with three mixtures: 50% fast-flo lactose and 50% Avicel 102, 50% Avicel 102 plus regular lactose and last mixture consist 50% of Avicel 101 and regular lactose. The aim of the study was to examine the behaviour of the flowability for different combinations of normally used materials, and to create a range of standard materials with different flowability that can be used to study the impact of flow properties on relevant processes. The moisture absorption was monitored by recording the weight change as a function of time. The weight has changed in each substances differently. The lubricant does not have important influence on free flowing powders. But the lubricant improves the flow properties of powders when the powder cohesion increases.

E. Schwarz et al. [27] investigated the effect of the lubricant on the disintegration time of a physical blend vs. the coprocessed excipient. The tablet strength and ejection

force were also reported. The materials used in the study were maize starch, cellulose powder, lactose monohydrate, MS, sodium stearylfumarate (SSF) and glyceryl dibehenate (GB). A top bottom spray was used for spray drying. The lubrication concentration was between 0.1% - 3.0% and the mixing time was 5 min. The tablets were compressed on a single punch press. The physical mixture of cellulose powder and lactose shows that with increasing lubrication concentration of GB and SSF decreases the ejection force, but not considerably with MS. The physical mixture of lactose and corn starch needs a higher lubrication level. With a higher lubrication concentration of GB the ejection force was decreased. MS and SSF did not have this significant influence. Magnesium stearate had the best lubrication properties for all the formulations. MS had also a great influence on the increasing time of the disintegration and lowering the tablet is hardness.

The study of micronized poloxamer 407 and poloxamer 188 as a lubricants in direct compression of tablets in combination with the spray-dried lactose and with the dry binders microcrystalline cellulose was the subject of interest of the Czech scientists led by Jitka Mužíková et al. [28] Magnesium stearate was used for comparison of the lubrication effect and all parameters, which were under examination. The watched parameters were ejection force, energy for friction, disintegration time, tensile strength and plasticity of tablets. Compression force, mixing time and frequency of mixing and concentration of lubricants influenced the results. Each of the binders was mixed with each lubricant in concentrations of 1 and 2%. The mixing time was 2.5 and 5 min with a frequency of mixing of 17 and 34rpm. The research shows that with a compression force the friction was increased for both dry binders. The ejection force was higher with the addition of compression force in Flowlac 100. However for microcrystalline cellulose there were values of ejection force lower. The lowest values of ejection force were in mixtures with magnesium stearate with both of the dry binders. The reason is that microcrystalline cellulose has its own lubricating effect. Lowers values of the ejection force were again found in the mixtures with MS and in its higher concentration. The energy of friction did not have a significant difference in mixture with both binders but it changes with changing parameters of mixing. In case of magnesium stearate the values little bit decreased with the mixing time and frequency. But the values increased slightly in poloxamers. Another object of study was the tensile strength. In Flowlac 100 were the lowest strength for MS. The strongest tablets were in blend with 2% poloxamer 407

compressed by force 12 kN. There were no significant differences with a changing concentration of the lubricants. About the tensile strength in Microcel MC – 102, the strength of the tablet was lower with a higher concentration of the lubricants. Disintegration time was increased by increasing concentration of lubricants and by compression force in both dry binders. This fact is related with the hydrophilic character of the poloxamers and decreased tensile strength.

Ribet et al. [29] studied different textures of talc grade: microcrystalline, macrocrystalline and moderately macrocrystalline. They researched the influence of the talc specific parameters (D50, texture, specific surface) on lubrication during making tablets and also on tablet mechanical properties (residual die pressure, lubrication index, and maximum ejection pressure). The mean diameter of talc was from 0.62 to 15 μm. The base formula for tablets with low lubrication properties contains 40% of microcrystalline cellulose, 45% of lactose and 15% of starch. Blends were mixed for 10 min in turbula mixer. Tablets were made with 3% of talc with a constant weight of 350 mg and about 3 mm high. The results represent an average of 10 measurements. The residual die force was constant with increasing of specific surface area, but the hardness of the tablet decrease with every texture of talc. The lubrication index improves with the increase of the specific surface area and reaches the value 0.8. The reduction of wall and particle friction is correlated with the increase of the specific surface area, which creates antiblocking properties to talc. When they examined talc texture, they found that behaviour of moderately macrocrystaline talcs is close to macrocrystalline. For D50>5 μm the talc texture influences compression parameter and tablet hardness. They observed a reduction in residual die pressure and also in ejection pressures compared to base formula. Microcrystalline talcs were more efficient than macrocrystalline ones. When D50<5 μm, results became equivalent. Textures converged because of the crushing. However the inclusion of talcs positively influences the tablet hardness and compression characteristics of the tablets, microcrystalline talcs have greater influence on it. The smaller D50 the greater lubrication effect. In the end they noticed that specific surface area is more relevant parameter to determine the lubrication ability.

Flament from France et al. [24] characterized different talcs and then evaluated them in decreasing sticking in tablet production. They compared talcs before and after delamination. The delamination is a method how to obtain talcs with different physical characteristics. This process reduced initial layers of talc lamellae by tangential shearing

and new basal surfaces were produced. The presence of new surfaces can influence the antisticking power of talc. A base for measuring was Avicel PH 102 (microcrystalline cellulose) and it was mixed with 1 or 3% of talc for 5 min in Turbula blender at 54 rpm. The position of upper punch was adjusted to give the tablets with hardness of 180 N with 1% of talc and 160 N for 3% of talc. The hardness was measured on 10 tablets. For all the experiments the tablet machine was adjusted in the same conditions. Measurements were carried out under conditions fo 20°C and 20% of relative humidity. The research confirms that efficiency of talc against sticking in blends with Avicel is related to the mean of surface diameter of particles. The different talcs had significant variation in antisticking power towards Avicel. Some of them did not meet any functionality of lubrication and even increase friction and adherence of tablets to the lower punch of the tablet machine. The result showed that for the effectiveness of talc as lubricant and antisticking agent an element delamination is not essential. But it should be continued with the classification of talc in different granulometric classes.

Almaya, Aburub et al. [19] studied the effect of excipient particle size on compaction properties. They used a few materials with different deformation mechanisms: brittle (dibasic calcium phosphate dihydrate), plastic (microcrystalline cellulose/MCC), and viscoelastic (starch) with and without lubricants. Magnesium stearate as a lubricant was used in concentration 0.5%. The lubrication effect on compact strength depends on a few factors such as concentration, mixing time or specific surface area. Powders were mixed with MS for either 5 or 30 min. The compact weight was 400 ± 2mg. It was used 10.3 mm flat faced punches. Generally the effect of mixing time on tablet crushing strength decreased with increasing particle size. The tablet strength of starch compacts decreases in the presence of lubricant and its more obvious with longer mixing time. The lower tablet strength is greater when the initial particle size of starch is larger. Microcrystalline cellulose is less sensitive to lubrication addition than starch, but the effect is the same. On the other hand the dibasic calcium phosphate dihydrate is independent of lubricant addition and lubricant mixing time. This is cause by brittle characteristic of material. Lubricant film on powders is disrupted upon compression, since new surfaces are generated because of fracture brittle material. In conclusion viscoelastic as well as plastic deforming materials are more sensitive to lubricant than brittle materials.

5 Experimental part

5.1 Materials

The following materials were used in this research.

Lactose monohydrate

Manufacturer: ALPAVIT Kaserei champignon Hofmeister GmbH, Germany

Batch number: Lote 130178-P-1

Magnesium stearate

Manufacturer: Kemilub EM – F, Spain

Batch number: 62861

Micro Talc Pharma 8 - AW

Manufacturer: Mondo Minerals B.V., Netherlands

Batch number: 11/0034

Micro Talc Pharma 50

Manufacturer: Mondo Minerals B.V., Netherlands

Batch number: 1200803

Micro Talc Pharma 30 – AW

Manufacturer: Mondo Minerals B.V., Netherlands

Batch number: 11/0946

Polyvinylpyrrolidone (PVP, Povidone)

Manufacturer: Fagron Iberica S.A.U., Spain

Batch number: L12120044-OF-113524

5.2 Equipment

Turbula mixer

Manufacturer: WAB T2F, Switzerland

Oscillating granulator

Manufacturer: Erweka® FGS, Germany

Fluid bed drier

Manufacturer: Glatt® 7859, Switzerland

Eccentric tablet press

Manufacturer: DOTT Bonapace, CPR-6, Italy

Tablet hardness tester

Manufacturer: Erweka TBH 28, Erweka GmbH, Germany

Analytical balance

Manufacturer: Mettler AE 200, Mettler Toledo, Switzerland

Particle size analyser Malvern-MasterSizer 3000

Manufacturer: Malvern Instruments Ltd, Worcestershire, UK

5.2.1 Methods

Preparation of granules

Granules were prepared by wet granulation. The blend consisting of 95 % of lactose (diluent) and 5 % of PVP (binder) was mixed in a Turbula mixer (WAB T2F, Switzerland) for 10 minutes. An oscillating granulator (Erweka® FGS, Germany) with a sieve of 1.6 mm at 220 rpm was used to granulate wet mass. Purified water was used as a granulating liquid. The granules were dried in a fluid bed drier (Glatt® 7859, Switzerland) and calibrated with a sieve of 1 mm at 220 rpm using Erweka® FGS. Obtained granules were mixed with 1%, 3%, 5%, 7% or 10% of talc for 5, 10, 15 and 20 minutes in the same Turbula® mixer. Other mixtures were prepared by blending the granules with 1%, 2% and 3% of magnesium stearate for 10 or 20 minutes in the Turbula® mixer. Total number of mixtures was 67 (20 for each type of talc, 6 for Magnesium stearate and 1 with granulate without lubricants).

Particle size determination

Particle size of magnesium stearate, Microtalc 8, 30 and 50 were determined by laser diffraction using a particle size analyser Malvern-MasterSizer 3000. This laser diffraction method is based on the spatial distribution of scattered light, which is a function of the particle size of the analysed sample. Sizes were determined using Mie theory with refractive index of 1.56 for talc and 1.45 for magnesium stearate. For the two materials the absorption index used was 0.1 and obscuration was between 5 and 10. The values of refractive index were found in Handbook of Pharmaceutical Excipients [14].

The Dv-10, Dv-50, Dv-90, D [3,2] and D [4,3] were obtained. Units for all of these values are in μm.

D 10 means, that 10 % of the particles are smaller than this diameter.

D 50 is a mean for volume distribution or an average of volume particle size. Number D 50 shows that 50% of particles are smaller and 50% are larger than this diameter.

D 90 expressed number where 90% of particles are smaller than this value and 10% of the distribution has a larger particle size.

D [3,2] is a surface area moment mean. It is the most sensitive for fine particles in distribution.

D [4,3] is a volume moment mean. It is the most sensitive to the presence of large particles.

Figures 6, 7 and 8 show how the MasterSizer 3000 displays the results in case of Microtalc 30:

	Record Number	Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)	Laser Obscuration (%)
	2	MicroTalc_30_6.10.new	4.66	16.1	41.0	5.69
	1	MicroTalc_30_6.10.new	4.69	16.2	41.0	5.65
	3	MicroTalc_30_6.10.new	4.66	16.1	41.3	5.70
	4	MicroTalc_30_6.10.new	4.65	16.2	41.9	5.72
	5	MicroTalc_30_6.10.new	4.65	16.2	41.8	5.73
	6	MicroTalc_30_6.10.new	4.64	16.2	42.0	5.71
	7	MicroTalc_30_6.10.new	4.63	16.1	41.6	5.70
	8	MicroTalc_30_6.10.new	4.64	16.2	42.0	5.71
	9	MicroTalc_30_6.10.new	4.63	16.2	41.8	5.70
	10	MicroTalc_30_6.10.new	4.63	16.2	41.9	5.68
Mean			**4.65**	**16.2**	**41.6**	**5.70**
1xStd Dev			**0.0181**	**0.0221**	**0.387**	**0.02**
1xRSD (%)			**0.388**	**0.137**	**0.929**	**0.39**

Fig. 6 Illustration of MasterSizer 3000 – the table of particles sizes Microtalc 30 averages

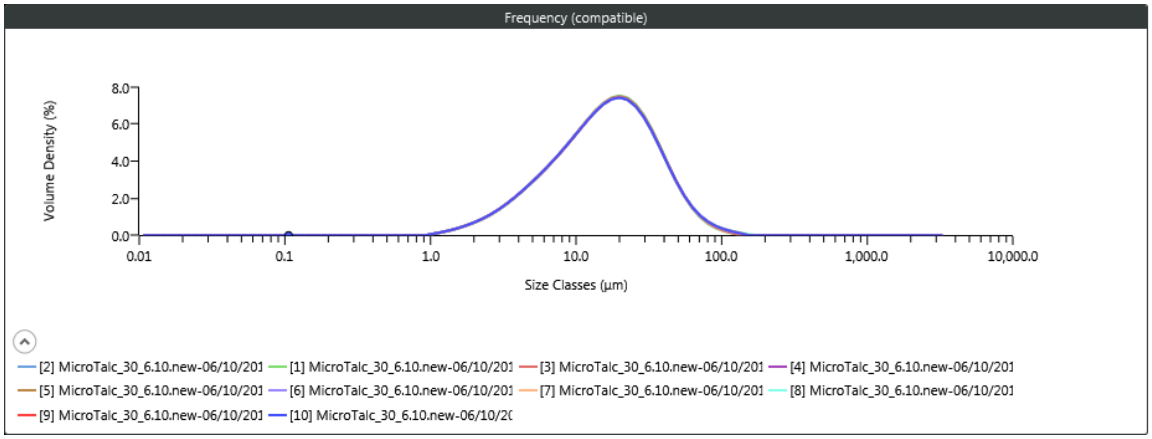

Fig. 7 Illustration of MasterSizer 3000 – the graph of particles sizes Microtalc 30

Result

Concentration 0.0071 %	**Span** 2.254
Uniformity 0.716	**Result Units** Volume
Specific Surface Area 592.0 m^2/kg	**Dv (10)** 4.66 µm
D [3,2] 10.1 µm	**Dv (50)** 16.1 µm
D [4,3] 20.3 µm	**Dv (90)** 41.0 µm
	Span (80,20) 1.443
	Residual 0.28 %
	Weighted Residual 0.55 %

Fig. 8 Illustration of MasterSizer 3000 – the table with values for Microtalc 30

Granules size analysis

Analytical sieving is utilized to estimate particle size distribution for particles of size larger than about 75 µm. In this method the sieves are stacked from the top to the bottom by ascending degrees of coarseness. Spectrum of granules particle size is defined via the mass on sieves.[30]

Sieves 1mm, 710 µm, 500 µm, 250 µm, 180 µ and 125 µm were used. The amount of sample was 25 g. Agitation was standardized to 10 min and amplitude was 2mm. The weight percentage of granules in each sieve was calculated. As can be seen in Figure 9, granules size was mostly around 250 µm, which was maintained for the entire measuring.

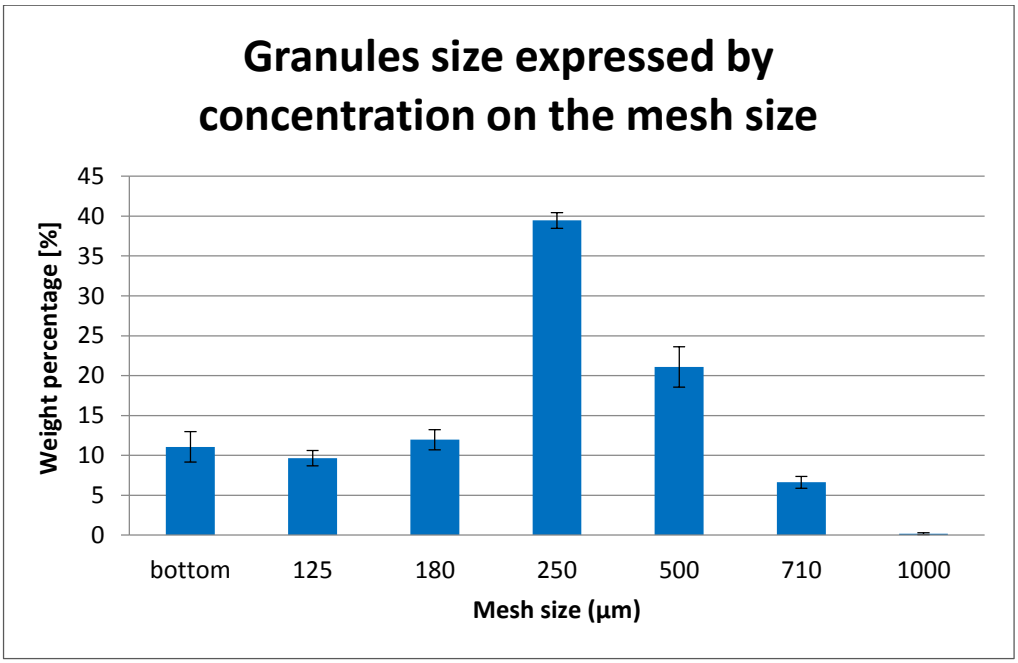

Fig. 9 Granules size expressed by granules weight percentage on the mesh size

Compression of granules

Tablets were manufactured by using an instrumented eccentric tablet press (DOTT Bonapace, CPR-6, Italy). The tablet press was coupled with a computer containing software Cosalt-write, Cosalt-read and FIMA Compression Data Analysis. Force of the upper and lower punch was measured.

The operation conditions were following:

- Flat punches of 11 mm diameter
- Upper punch displacement adjusted to 5 mm
- Press speed of one tablet in one second

Tablet hardness

Tablet hardness was measured on 10 tablets after 24 hours (Erweka TBH 28, Erweka GmbH, Germany).

Tablet average weight was 390 mg.

Lubrication index (LI)

The computer was connected with the tablet press DOTT Bonapace using software Cosalt-write, Cosalt-read and FIMA Compression Data Analysis. Thanks to this software the compression curves could be registered. Illustration of the compression curve is in figure 10. It was also possible to measure energies and forces exerted during compaction, and to evaluate the time periods of the force/time cycle of compression.

R-value or lubrication index (LI) is ratio of the maximum lower and upper punch forces. Lubrication index is used for comparing lubricants. The higher the number, the better the lubricant. The maximum value is 1.

LI was calculated according to the following equation 1 [7]:

$$\mathbf{R} = F_I / F_S \quad (1)$$

Where F_I is force applied on the lower punch and F_S is force applied on the upper punch. Lubrication index was measured on 10 tablets from each batch.

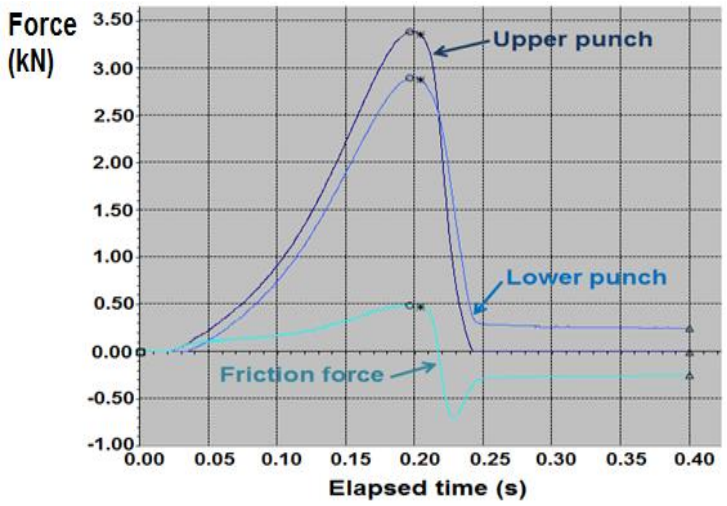

Fig. 10 Ilustration of FIMA Compression Data Analysis

5.3 Tables

The following tables express the mean of the values obtained in the study. Each value expresses the mean of the 10 tablets made under the same conditions. The volume of the compression chamber and the upper punch displacement were maintained constant during experiments. Values in the tables show general overview. Results are discussed and explained in more details in the chapter Results and discussion.

Table 1 The summary values for magnesium stearate and base granules

	Mixing time [min]	**MD [mm] - point of maximum upper punch displacement**	**Hardness [N]**	**Force of upper punch [kN]**	**Force of lower punch [kN]**	**Lubrication index**
Lactose + PVP		4.93	15	4.01	2.6	0.65
MS						
1%	10	4.81	33.7	7.36	7.18	0.98
	20	4.81	42.8	8.42	8.24	0.98
2%	10	4.91	18.9	4.13	4.04	0.98
	20	4.89	26.8	5.77	5.59	0.97
3%	10	4.82	25.3	5.53	5.27	0.95
	20	4.9	26.2	5.49	5.24	0.95

Table 2 The summary values for Microtalc 8

Microtalc 8	**Mixing time [min]**	**MD [mm] - point of maximum upper punch displacement**	**Hardness [N]**	**Force of the upper punch [kN]**	**Force of the lower punch [kN]**	**Lubrication index**
1%	5	4.86	18.7	6.55	4.37	0.67
	10	4.97	14.5	4.13	2.54	0.62
3%	5	5.09	33.8	7.27	5.95	0.82
	10	4.83	47.9	10.05	7.93	0.79
	15	4.92	50.4	10.01	7.89	0.79
	20	4.95	72.1	11.5	9.15	0.80
5%	5	4.73	41.2	7.76	6.57	0.85
	10	4.84	41	8.64	7.04	0.81
	15	4.84	50.6	9.24	7.37	0.80
	20	4.98	141.4	10.55	8.33	0.79
7%	5	4.98	39	7.76	6.74	0.87
	10	5.04	32.8	6.78	5.8	0.86
	15	4.85	69	11.4	9.46	0.83
	20	5.01	69	12.42	10.21	0.82
10%	5	4.99	23.2	4.72	4.39	0.93
	10	5.01	32.7	6.1	5.49	0.90
	15	4.88	45.8	7.91	6.84	0.86
	20	4.93	46.6	8.69	7.52	0.87

Table 3 The summary values for Microtalc 30

Microtalc 30	Mixing time [min]	MD [mm] - point of maximum upper punch displacement	Hardness [N]	Force of the upper punch [kN]	Force of the lower punch [kN]	Lubrication index
1%	5	4.98	22.4	5.44	3.95	0.73
	10	4.97	19.6	5.26	3.61	0.69
	15	4.97	16.4	4.12	2.78	0.67
	20	5.02	21.6	5.55	3.64	0.66
3%	5	4.88	26.3	6.87	5.29	0.77
	10	4.91	33.1	7.36	5.74	0.78
	15	4.94	33	7.26	5.55	0.76
	20	4.92	47.1	9.94	7.45	0.75
5%	5	4.98	23.8	5.88	5.04	0.86
	10	4.94	32.3	7.62	6.35	0.83
	15	4.97	31.9	7.07	5.78	0.82
	20	4.84	52.4	11.07	8.83	0.80
7%	5	4.96	29.5	7.36	6.07	0.82
	10	4.86	34.5	8.31	6.79	0.82
	15	4.86	42.5	9.35	7.93	0.85
	20	4.92	52.3	10.65	8.99	0.84
10%	5	4.96	27.7	7.34	6.39	0.87
	10	4.85	32.9	8	7.43	0.93
	15	4.88	49.7	10.91	9.48	0.87
	20	4.95	55.2	12.14	10.38	0.86

Table 4 The summary values for Microtalc 50

Microtalc 50	**Mixing time [min]**	**MD [mm] - point of maximum upper punch displacement**	**Hardness [N]**	**Force of the upper punch [kN]**	**Force of the lower punch [kN]**	**Lubrication index**
1%	5	4.99	17.2	4.85	3.58	0.74
	10	5	17.4	5.04	3.62	0.72
	15	4.95	17.7	5.17	3.59	0.69
	20	4.98	17.7	5.92	3.94	0.67
3%	5	4.88	25	6.9	5.3	0.77
	10	4.94	31.3	8.29	6.22	0.75
	15	4.97	43.9	9.44	7.18	0.76
	20	4.97	46.3	10.75	8.01	0.75
5%	5	4.93	22.3	6.28	5.14	0.82
	10	4.94	31	7.43	6.16	0.83
	15	4.84	44.5	9.83	7.87	0.80
	20	4.8	46.4	9.98	7.97	0.80
7%	5	5.01	26.7	7.38	6.12	0.83
	10	4.97	32.8	7.71	6.38	0.83
	15	4.93	46.1	9.96	8.37	0.84
	20	4.99	59.4	11.45	9.44	0.82
10%	5	5.01	24.9	6.95	6.04	0.87
	10	4.98	31.9	8	6.92	0.87
	15	4.81	42.9	9.74	8.27	0.85
	20	4.95	48.9	11.15	9.33	0.84

5.4 Results and discussion

5.4.1 Lubrication index

Magnesium stearate

Lubrication index of lactose granules without any lubricants was 0.65. As illustrated in Table 5, the values of lubrication index of granules with MS were higher than lactose granules. Values almost reach 1, which means that MS is a significantly effective lubricant. However, lubrication index does not increase with the increasing concentration of MS. As the results suggest, higher concentration of magnesium stearate does not necessary mean higher lubrication effect productivity. Values are expressed with their relative standard deviation.

Table 5 The effect of magnesium stearate concentration on the lubrication index (mixing time: 10 minutes)

MS [%]	Lubrication index
1%	0.98 ± 0.003
2%	0.98 ± 0.019
3%	0.95 ± 0.005

Table 6 shows that mixing time has almost no effect on lubrication index in case of magnesium stearate. For example, at 1% of MS and 10 minutes of mixing time the lubrication index is the same as with 20 minutes. In case of 2% the change is not relevant either. It is not necessary to prolong mixing time for granules with magnesium stearate in order to reach a sufficient lubrication effect.

Table 6 The effect of mixing time on the lubrication index of magnesium stearate

MS [%]	Mixing time [min]	Lubrication index
1	10	0.98 ± 0.003
	20	0.98 ± 0.002
2	10	0.98 ± 0.019
	20	0.97 ± 0.005

Microtalc

Lubrication index increases with the increasing concentration of talc. As shown in Table 7, the mixture of 1% of Microtalc 8 reaches a lubrication index of 0.62 ± 0.026 (in 10 minutes of the mixing), if the concentration is increased to 10%, the values reach 0.9 ± 0.007 (in 10 minutes of the mixing).

Table 7 The effect of Microtalc 8 concetration on the lubrication index (mixing time: 10 minutes)

Microtalc 8 [%]	Lubrication index
1	0.62 ± 0.026
5	0.81 ± 0.003
10	0.9 ± 0.007

After 15 minutes of mixing, the mixture of 1% of Microtalc 8 exhibits a noticeably higher friction. So we could not measure lubrication index for this time. The lower amount of lubricant is an audible characteristic for its screeching sound. It results in additional strains on the machine parts. Increased friction could be the reason of poor mixing results. Small particles of Microtalc 8 powder did not coat the granules made from lactose and PVP sufficiently. As can be seen in Table 8, with the higher concentration of Microtalc 8, it is easier to get a better distribution of talc, and it is not necessary to increase mixing time. Higher mixing time does not produce higher lubrication index.

Table 8 The effect of mixing time on the lubrication index of Microtalc 8

Microtalc 8 [%]	Mixing time [min]	Lubrication index
1	5	0.67 ± 0.008
	10	0.62 ± 0.026
3	5	0.82 ± 0.004
	10	0.79 ± 0.001
	15	0.79 ± 0.039
	20	0.8 ± 0.004
5	5	0.85 ± 0.006
	10	0.81 ± 0.003
	15	0.8 ± 0.002
	20	0.79 ± 0.003

In the case of Microtalc 30 the lubrication index also gets higher with the increasing concentration of talc. Table 9 demonstrates that the lubrication index increases from 0.69 ± 0.029 to 0.93 ± 0.021 while concentration increases from 1% to 10% of Microtalc 30.

Table 9 The effect of Microtalc 30 concetration on the lubrication index (mixing time: 10 minutes)

Microtalc 30 [%]	Lubrication index
1	0.69 ± 0.029
5	0.83 ± 0.003
10	0.93 ± 0.021

As it can be seen in Table 10, the mixing time does not have a great effect on the lubrication index. The lubrication index decreases slightly with increasing mixing time.

Table 10 The effect of mixing time on the lubrication index of Microtalc 30

Microtalc 30 [%]	Mixing time [min]	Lubrication index
1	5	0.73 ± 0.020
	10	0.69 ± 0.029
	15	0.67 ± 0.044
	20	0.66 ± 0.007
3	5	0.77 ± 0.011
	10	0.78 ± 0.005
	15	0.76 ± 0.010
	20	0.75 ± 0.008
5	5	0.86 ± 0.007
	10	0.83 ± 0.003
	15	0.82 ± 0.002
	20	0.8 ± 0.003

The effect of the concentration of Microtalc 50 on LI is displayed in Table 11. The ability of Microtalc 50 to increase LI rises with its concentration.

Table 11 The effect of Microtalc 50 concentration on the lubrication index (mixing time: 10 minutes)

Microtalc 50 [%]	Lubrication index
1	0.72 ± 0.044
5	0.83 ± 0.024
10	0.87 ± 0.016

Table 12 shows the effect of mixing time on the lubrication index. In fact, mixing time does not have any significant influence on the resulting lubrication index.

Table 12 The effect of mixing time on the lubrication index of Microtalc 50

Microtalc 50 [%]	Mixing time [min]	Lubrication index
1	5	0.74 ± 0.024
	10	0.72 ± 0.044
	15	0.69 ± 0.033
	20	0.67 ± 0.022
3	5	0.77 ± 0.012
	10	0.75 ± 0.002
	15	0.76 ± 0.025
	20	0.75 ± 0.030
5	5	0.82 ± 0.013
	10	0.83 ± 0.024
	15	0.80 ± 0.002
	20	0.80 ± 0.017

5.4.2 Hardness

Magnesium stearate

As we can see in Table 13, tablet hardness is decreasing with increasing concentration of magnesium stearate. The difference at 1% and 2% is technologically relevant, but at 2% and 3% the difference is very small and we can consider that hardness is not changing. The highest tablet hardness is in case of magnesium stearate 1%. The decrease in hardness is due to weak bonds between molecules of lubricant after compression. Lubricating film over the granules interferes with the binding of the particles. Tablet strength is affected by the amount of lubricant.

The numbers in brackets express range of values for tablet hardness. A wide range of the values can be caused by the machine itself, because it was a quite old tester of the tablet hardness, which sometimes gives a deviation values.

Table 13 The influence of concentration on the tablet hardness with magnesium stearate (mixing time: 10minutes)

MS [%]	Hardness [N]
1	33.7
	(25-38)
2	18.9
	(9-25)
3	25.3
	(19-30)

The influence of mixing time on hardness can be seen in Table 14. The tablet hardness increases with longer mixing time.

Table 14 The influence of mixing time on the tablet hardness with magnesium stearate

MS [%]	Mixing time [min]	Hardness [N]
1	10	33.7
		(25-38)
	20	42.8
		(39-46)
2	10	18.9
		(9-25)
	20	26.8
		(23-30)

Microtalc

Table 15 shows that the tablet hardness increases with higher concentration of Microtalc 8. But in concentration of 10% of talc the hardness suddenly decreased. It can be caused by a high amount of fine particles of lubricant inside the mixture. So after exceeding the certain amount the hardness will decrease.

Table 15 The influence of concentration on the tablet hardness with Microtalc 8 (mixing time: 10minutes)

Microtalc 8 [%]	Hardness [N]
1	14.5
	(10-18)
3	47.9
	(34-64)
10	32.7
	(25-36)

Hardness of tablets where Microtalc 8 was used as a lubricant increases with increasing mixing time (Table 16). For example in 5% concentration of MicroTalc 8 the hardness increases from 41 N (in 10-minute mixing time) to 50.6 N (in 15 minutes).

Table 16 The influence of mixing time on the tablet hardness with Microtalc 8

Microtalc 8 [%]	Mixing time [min]	Hardness [N]
3	10	47.9
		(34-64)
	15	50.4
		(35-68)
5	10	41
		(25-48)
	15	50.6
		(41-58)
10	10	32.7
		(25-37)
	15	45.8
		(42-49)

The influence of the concentration of Microtalc on the tablet hardness is presented in Table 17. Tablet hardness grows with increasing concentration from 1% to 3% for Microtalc 30. But after exceeding 3% of concentration tablet hardness is almost constant

and values are not considerably changing. If we increase the amount of the lubricant, the hardness will probably decrease, as it is described in literature.

Table 17 The influence of concentration on the tablet hardness with Microtalc 30 (mixing time: 10minutes)

Microtalc 30 [%]	Hardness [N]
1	19.6
	(15-23)
3	33.1
	(25-37)
10	32.9
	(27-39)

As the Table 18 shows the mixing time does not influence tablet tensile strength in 10 and 15 minutes which are the most commonly times used for mixing. But if we look at the change from 5 to 20-minute mixing time in the summary tables at the begining, we can see a small increase in tablet hardness.

Table 18 The influence of mixing time on the tablet hardness with Microtalc 30

Microtalc 30 [%]	Mixing time [min]	Hardness [N]
3	10	33.1
		(25-37)
	15	33
		(27-40)
5	10	32.3
		(22-44)
	15	31.9
		(21-37)
10	10	32.9
		(27-39)
	15	49.7
		(36-58)

Table 19 shows the effect of concentration of Microtalc 50 on tablet strength. Hardness grows from 1% of concentration to 3%, but when we reach this concentration the tablet hardness remains unchanged and ranges in similar values.

Table 19 The influence of concentration on the tablet hardness with Microtalc 50 (mixing time: 10minutes)

Microtalc 50 [%]	Hardness [N]
1	17.4
	(14-24)
3	31.3
	(21-36)
10	31.9
	(25-37)

In Table 20, with Microtalc 50 we can clearly see the effect of mixing time on tablet strength. With every Microtalc we used the tablet hardness increases with higher mixing time.

Table 20 The influence of mixing time on the tablet hardness with MicroTalc 50

Microtalc 50 [%]	Mixing time	Hardness [N]
3	10	31.3
		(21-36)
	15	43.9
		(38-50)
5	10	31
		(25-34)
	15	44.5
		(33-49)
10	10	31.9
		(25-37)
	15	42.9
		(30-47)

5.4.3 Particle size

In the following Table number 21, we can see the different values for particle size for the every type of lubricant used in this study. These values were obtained by MasterSizer 3000 using the laser diffraction. Results show that the magnesium stearate has the biggest particle size and the second one is Microtalc 50.

Table 21 Partciles sizes of used lubricatns

type of the lubricant	D 10 [µm]	D 50 [µm]	D 90 [µm]	Specific surface area m²/kg	D [3,2] (µm)	D[4,3] (µm)
Magnesium stearate	5.73	38.6	107	522.5	11.5	49.6
Microtalc 8	2.67	6.9	28	1196	5.01	9.5
Microtalc 30	4.65	16.2	41,6	592	10.1	20.3
Microtalc 50	5.51	24.6	75,8	457.9	13.1	33.8

In the following Table 22, you can see the effect of particle size to tablet strength. The hardness of tablets with Microtalcs is changing in case of Microtalc 8 and Microtalc 30. Until we have a D 50 level of 16.2 µm the hardness variation is considerably significant (changing from 47.9 N to 33.1 N) but when the size of particles increases to 24.6 µm the variation is not relevant and the values of hardness are almost the same. Even magnesium stearate with particle size 38.6 µm has very similar values.

Table 22 The effect of particle size to tablet hardness with lubricants (mixing time: 10 minutes)

Lubricants	D 50 [μm]	Concentration [%]	Hardness [N]
MS	38.6	1	33.7
			(25-38)
		3	25.3
			(19-30)
Microtalc			
8	6.9	1	14.5
			(10-18)
		3	47.9
			(34-64)
30	16.2	1	19.6
			(15-23)
		3	33.1
			(25-37)
50	24.6	1	17.4
			(14-24)
		3	31.3
			(21-36)

As the Table 23 shows the results found for the lubrication index are not influenced by particle size very much. The variation of the lubrication index is not considerable when the mean of D 50 of Microtalcs increases. For example, when D 50 of Microtalc 8 is 6.9 μm the lubrication index is 0.79, and if we compare it with Microtalc 50 which has almost four times higher D 50, the lubrication index is 0.75 in 3% of concentration. These numbers prove that there is not a significant variation. Only magneisum stearate with higher particle size has better lubricating effect but it is a different compound, so there can be more reasons why it is much better lubricant.

Table 23 The effect of particle size to the lubrication index with Microtalcs (mixing time: 10 minutes)

Lubricants	D 50 [μm]	Concentration [%]	Lubrication index
MS	38.6	1	0.98 ± 0.003
		3	0.95 ± 0.005
Microtalc			
8	6.9	1	0.62 ± 0.026
		3	0.79 ± 0.001
30	16.2	1	0.69 ± 0.029
		3	0.78 ± 0.005
50	24.6	1	0.72 ± 0.044
		3	0.75 ± 0.002

5.5 Conclusion

As the results suggest, only a small amount of lubricant is needed to reduce the friction effectively. Tablet lubricants interfere between particles and the die wall and create a film on the granules, which reduces the friction force. If the lubrication index reaches values above 0.8, its effect can be considered as adequate. An example of such lubricant is magnesium stearate which produced such results in every concentration and mixing time. Lubrication index reaches 0.98 with 1% magnesium stearate in 10 minutes of mixing time already. On the other hand, talc exhibited sufficient lubrication effect with concentration of 3% and higher. Maximum values for talc reach 0.93 with 10% of Microtalc 8 and Microtalc 30. It was found out that short mixing time is sufficient to achieve a good lubrication.

Tablet hardness in general decreases with longer mixing time, but it depends on other conditions and the ingredients. The decrease is caused by new bonds between lubricant-lubricant that appear after compression. Such bonds are considerably weaker. For this reason, a bigger amount of the lubricant caused production of tablets with lower hardness. The mixtures with magnesium stearate exhibited decreasing tablet strength with the increasing amount of the lubricant. Mixing time did not have a significant effect on the hardness. In the case of talc, tablet hardness increased with longer mixing time. This phenomenon can be caused by fragmentation of lactose. With longer mixing time lactose breaks down into smaller pieces and is not sufficiently coated by talc. This is also the reason of the lower lubrication effect after prolonged mixing time. Increasing concentration of talc improved tablet strength until some point at which the strengthening stopped. It is very likely to have the opposite effect after reaching a certain concentration because of the weak bonds between lubricants.

The relationship between force of the upper punch and the tablet hardness was observed, but the result was not consistent. The influence of variation in particle sizes of lubricants on the lubrication index was minimal as well as for the tablet hardness. Magnesium stearate with the largest particle size has the most satisfactory values for the lubrication index, but it is also a different compound compared with talc. Different types of the Microtalc´s do not have noticeable distinction in values. The concentration of talc has to be higher to obtain satisfactory values for lubrication index. Nevertheless, a shorter mixing time is sufficient to obtain an adequate lubrication of Microtalc. In case of

magnesium stearate it is not necessary to increase the concentration. Magnesium stearate is an efficient lubricant in a small amount and with short mixing time.

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