Lubricants and sensitivity of dry binders to lubricants added to tableting materials

Lubricants decrease friction during compression, prevent adhesion of tableting material to the punches and walls of the matrix, improve pushing-out of the tablet from the matrix after compression. Lubricants may also perform the function of the glidant, which improves the flowability of tableting material, which achieves a continuous filling of the matrix, resulting in mass uniformity of tablets. In the production of tablets, lubricants are added only in a small amount, the usually sufficient concentration is 0.25 % - 5.0 %.
Lubricants can act by two mechanisms:

- Liquid (hydromechanical – in this type of lubrication, two surfaces move separated with a layer of the lubricant. This mechanism can be carried out by mineral oils. These oils, however, are rarely used in tablet manufacture because even a very little dispersion produces fat spots of tablet surface.

- Contact (touch) – in contact lubrication, the effect is based on the adhesion of the polar part of the lubricant to the metal surface of the punches and matrix, covered with a fine film of metal oxides.

Lubricans can be divided into hydrophobic and hydrophilic ones. Of the hydrophobic lubricants, the most widely used ones are stearates, i.e. magnesium stearate, calcium stearate, zinc stearate, and aluminum stearate, and also stearic acid and sodium stearyl fumarate. The hydrophilic lubricants include sodium lauryl sulphate, magnesium lauryl sulphate, and polyethylene glycols (PEG 4000, 6000).

Effects of lubricants can be evaluated by means of the ejection force which is the force required to push out the tablets from the matrix.

An addition of a lubricant into a directly compressible tableting material can very markedly influence the properties of tablets, such as their strength and disintegration time. A hydrophobic lubricant extends disintegration time of tablets. An addition of a powdered lubricant into a tableting mixture in the process of mixing results in the formation of a film of the lubricant on the particles of the other components of the tableting material. The formation of this film results in a decrease in tablet strength. The basic excipient which is in surplus in the directly compressible tableting material is a dry binder. The intervention of the lubricant into the strength of bonds strongly depends on the mechanism of its compression. A dry binder which is compressed by the mechanism of plastic deformation (e.g. starches, microcrystalline cellulose) is highly sensitive to an added lubricant. On the other hand, a dry binder (calcium

phosphates), which is compressed prevalently by fragmentation of particles, is not sensitive to an added lubricant, as in the course of compression there develop clean intersurfaces not covered with the film of the lubricant. Sensitivity to the addition of lubricants further depends on the type of the lubricant, its concentration, the presence of other substances in the mixture, on mixing conditions (rate, period of mixing) and on the type of the mixing device. From the practical viewpoint, the shortest period of mixing with the lubricant is suitable, so the lubricant is added into tableting material for a short period of mixing as late as at the end.

Sensitivity of a dry binder to an added lubricant can be expressed by means of the value LSR (lubricant sensitivity ratio), which can be calculated according to the equation:

LSR = (CSu – CSl) / CSu,

where CSu expresses the strength of tablets without a lubricant and CSl expresses the strength of tablets with a lubricant. The more the LSR value approaches the value of 1, the higher the sensitivity of the substance to lubricants and the lower the strength of tablets are.

Factors influencing the formation of the film of the lubricant

The nature of the lubricant

The effect of a lubricant on the binding properties of the initial particles in the formation of tablets depends on the nature of the employed lubricant. Decreased strength of tablets during mixing with lubricants has been demonstrated in the following lubricants: magnesium stearate, stearic acid, sodium stearyl fumarate, sodium lauryl sulphate, magnesium lauryl sulphate, and polyethylene glycol 4000. However, it has been observed that the effect on tablet strength is also influenced by the specific surface of the employed lubricants. Tablets with coarse sodium stearate were stronger than tablets containing a finer degree of the lubricant. Magnesium stearate forms strong adhesive interactions of the lubricant-dry powder type. These interactions explain the formation of a monomolecular film on the particles, which results in a decrease in strong adhesive interactions between the particles of dry binders and a decrease in tablet strength.

Concentration and specific surface of lubricants

An effect on tensile strength of tablets is also exerted by the concentration and specific surface of the lubricant used. Using a low concentration of magnesium stearate, the formation

of the film will be slower and therefore also the decrease in tablet strength will be smaller for the given period of mixing while keeping the identical conditions of mixing in comparison with a higher concentration of the lubricant.

When mixing the excipients with large particles of magnesium stearate, there occurs deceleration of the process of the formation of the film in comparison with mixing with small particles of the lubricant. This can be the cause why the influence of granulated magnesium stearate on tablet strength is smaller than in powdered magnesium stearate. It is due to the fact that a fine powdered lubricant is transferred on the surface of the initial particles more, which results in decreased tablet strength. A negative effect of a granulated lubricant on tablet strength is increased in a longer period of mixing, or when the amount of the dose is increased. This effect was explained by reduction of the granules of stearate after a long period of mixing and higher share forces due to a large amount used.

Morphology and crystalline modification of lubricant

There exist great differences between the individual batches of magnesium stearate, differing in both chemical and physical properties. To determine the rate and extent of covering the surface of particles with a lubricant, chemical differences, structural and crystalline properties of the lubricant are employed.

A fundamental difference appeared between commercial magnesium stearate and magnesium stearate of high purity, as far as covering of the surface of the particles is concerned. Commercial samples cover the initial particles in a much larger extent than the pure product. In addition, bad formation of the film with the use of pure products is attributed to its crystalline structure. The more crystalline and of high purity the lubricant is, the more resistant it is against gliding during the mixing process.

Effect of the initial material on the formation of the film of the lubricant

The precondition for the formation of a film of the lubricant on initial particles is the distribution of the particles of the lubricant between the initial particles. The flow properties of the initial particles and their size exert influence on the rate with which the film of the lubricant is formed. If the flow properties are bad, the distribution of the particles of the lubricant and the subsequent formation of the film during mixing will be very slow.

Effect of operating conditions on film formation

A negative influence of the lubricant on tablet strength does not depend only on the period of mixing, but also on the process itself. The effect of magnesium stearate on tablet strength was examined using different types of laboratory mixing devices. An important role is played by the time and intensity of mixing. If the production is on a larger scale, gliding forces are increased. It can thus be expected that in large devices the gliding forces which influence migration of the particles of magnesium stearate to the particles of excipients are much greater than in the laboratory mixing devices. This means that the formation of a film will depend on the type, size, load, and rate of the mixing devices used. A decrease in tablet strength in compressed tablets takes place markedly more rapidly in a manufacturing mixing device in comparison with laboratory mixers operating with an identical rate of rotation. A negative effect of the lubricant is also increased with the size of the amount, resulting from higher gliding forces in a mixer with a larger content.

Effect of the third component on film formation of the lubricant

Formation of a film of a lubricant during mixing can be influenced by a third component. Simultaneous mixing of particles of excipients with magnesium stearate and colloidal silicon dioxide (Aerosil 200) can significantly suppress the negative effect of the lubricant on binding properties. If the excipients are first mixed with colloidal silicon oxide prior to the addition of the lubricant, this effect is even more marked because of competitive inhibition of binding sites for stearate. On the other hand, an addition of silicon oxide after previous mixing of excipients with magnesium stearate can even restore the binding properties, in the case that the ratio between colloidal silicon oxide and magnesium stearate is 4:1. Even a low concentration (0.2 %) of silicon dioxide can suppress harmful effects of 0.5 % of magnesium stearate. If colloidal silicon oxide is mixed together with a lubricant, the coverage of the surface of the particles with the lubricant is decreased. Colloidal silicon dioxide functions as a glidant which can decelerate the formation of the film of magnesium stearate, if the tableting mixture is first mixed with colloidal silicon dioxide and then with magnesium stearate.

There exist various possibilities of limiting the undesirable effect of magnesium stearate on the properties of tablets without influence on the efficiency of lubrication:

- Exclusion of the lubricant and use of alternative methods of lubrication – there are mostly modifications of tableting devices for supplying the exact amount of suitable lubricant direct on the surface of the matrix and punches by means of special techniques. These methods are naturally relatively expensive.
- minimal concentration of the lubricant used
- selection of alternative lubricants
- change of the process of mixing – another possibility is a change of the process of mixing, when the active ingredients and excipients should be mixed as the first ones and without an added lubricant. After the addition of the lubricant, mixing should continue only for a short period of time.
- selection of a suitable dry binder – sensitivity of the lubricant can be decreased by proper selection of a suitable excipient, because the effect of magnesium stearate depends, besides other things, on the nature of the excipient. The highest decrease in tablet strength can be expected with the use of starches or cellulose; on the other hand, the least decrease in strength occurs in tablets containing fragile materials, such as calcium phosphate dihydrate or non-aqueous β-lactose.
- pre-mixing with colloidal silicon dioxide

Magnesium stearate

Summary formula: $C_{36}H_{70}MgO_4$

Description and properties

Magnesium stearate (Fig. 1) is obtained from both plant and animal sources. It is prepared by the chemical reaction of an aqueous solution of magnesium chloride with sodium chloride, or the reaction of magnesium oxide, hydroxide or carbonate with stearic acid in elevated temperature. Raw materials which are used for the preparation of magnesium stearate are refined fat acid, i.e. a mixture of stearic and palmitic acids. The content of magnesium is 4-5 % calculated for the dry base, fat acids are contained altogether up to 90 %, with the main content of stearic acid which amounts to more than 40 %.

Magnesium stearate is a very fine, light white powder. This powder is greasy to the touch and easily sticks to the skin. It slightly smells of stearic acid and possesses a characteristic taste. It is practically insoluble in water, ethanol and ether. Magnesium stearate is stable and should be kept in an air-proof vessel in a dry and dark place.

Magnesium stearate can produce a number of hydrates after exposure to humidity. Amorphous magnesium stearate has four states of hydration: anhydrate, monohydrate, dihydrate, and trihydrate. These states can reversibly pass from one another in dependence on temperature and relative humidity. For example, the non-aqueous form of magnesium stearate at the humidity above 70 % rehydrates giving rise to trihydrate. In dependence on the environment to which it was exposed, magnesium stearate from the supplier can be obtained as a mixture of anhydrate, hydrate, and an amorphous form. The efficacy of lubrication of stearate, of course, differs according to its hydration state. It generally holds true that dihydrate, thanks to its crystalline structure, is considered to be the most effective lubricant. The state of hydration of magnesium stearate also influences flowability, porosity, and compressibility of tablets. It generally holds true that tablets with stearate monohydrate possess the lowest permeability and porosity, followed by dihydrate and anhydrate. The structure of the lubricant exerts influence on the inner arrangement of particles and the mixtures containing monohydrate of the lubricant require higher compression forces in comparison with dihydrate and anhydrate. Besides the hydration state, effects on the efficacy of lubrication are also exerted by the properties of the powder themselves.

Magnesium stearate obtained from different suppliers or different batches possesses a different particle size, and different shape or surface of he particles. It is important to understand how these properties influence mechanical properties of compressed tablets and their dissolution. It is generally expected that efficacy of lubrication of magnesium stearate is improved with a decreased size of its particles and increased specific surface, because this increase can provide a larger coverage of the surfaces of the particles. Resulting from the larger coverage of the surfaces of particles with stearate, the bonds of the particles of the dry binder are weakened, which results in less strong tablets.

An addition of magnesium stearate generally improves the flowability of a powdered mixture. The flowability of the mixture is mainly influenced by the type of the lubricant, concentration, and the period of mixing with the lubricant. For example, in mixing lactose with a small amount of magnesium stearate, there occurs the greatest improvement in flowability in comparison with other lubricants (stearic acid, calcium stearate). The mechanism of this effect is interaction with the particles of lactose, when the particles of

stearate fill in the cavities of lactose particles. In addition, there occurs a decrease in the strength and prolongation of disintegration time of tablets compressed from a mixture of lactose and stearate. It is due to the fact that as soon as stearate produces a film on the particles, it is very difficult to erode it. The flowability of the resultant mixture is also influenced by the size and size distribution of the powdered mixture. Small particles can cause problems with flowability and covering of the particles with the particles of stearate. To effectively decrease the friction between the particles, the lubricant must be on their surfaces.

With regard to the manufacturing process, there exist various impurities of magnesium stearate (e.g. magnesium oxide). Magnesium stearate is incompatible with strong acids, bases, and salts of iron. Its mixing with an oxidizing material is not appropriate. It also causes incompatibilities with some drugs, e.g. it cannot be used in the preparations containing aspirin or some vitamins.

As magnesium stearate is hydrophobic, it can decelerate dissolution of solid dosage forms, that is why in these forms it is employed in the lowest possible concentration. Dissolution of active ingredients from tablets is influenced by the amount of magnesium stearate and also by the period of mixing with lubricant.

Use

Magnesium stearate is used as a glidant for tablets and capsules. In addition, it is employed in cosmetics (protective creams) and in foodstuffs it serves to bind sugar in hard sweets for children. It has been approved by the organization FDA (Food and Drug Administration) as a nontoxic substance routinely used in pharmaceutical industry for peroral administration. Nevertheless, its higher consumption may act in a laxative way or it may irritate the mucous membrane of the mouth.

Magnesium stearate is often used in tablets due to its lubricating properties. It is a very effective lubricant which is used at the low concentration of 0.25 –5 %. It prevents sticking of tableting material to the manufacturing device during compression of the mixture into tablets. The effect of concentration of magnesium stearate and the period of mixing with other components of the preparation are interrelated.

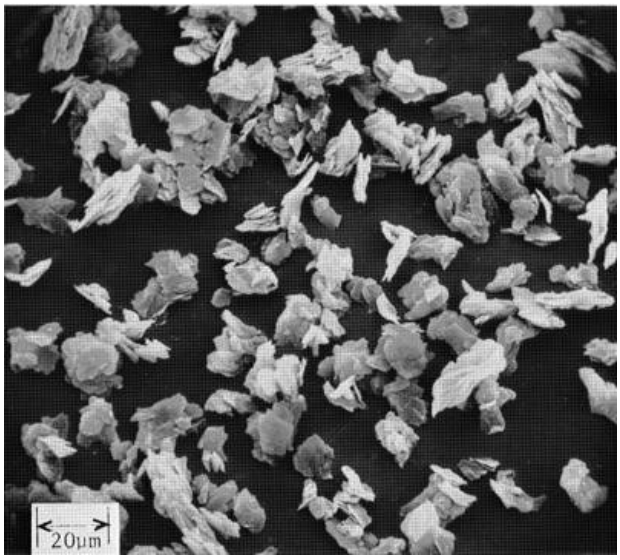

Fig. 1: Magnesium stearate (enlarged 600x)

Sodium stearyl fumarate

Summary formula: $C_{22}H_{39}NaO_4$

Description and properties

Sodium stearyl fumarate (Fig. 2) is a fine white powder consisting of agglomerates of the size of 5-10 µm. It is practically insoluble in ethanol, acetone, and chloroform. In water its solubility changes in dependence of the temperature of water: 1:20 000 at 25°C, 1:10 at 80°C, and 1:5 at 90°C. Typical properties of sodium stearyl fumarate are incompatibilities for sodium salts, above all with a higher share of water. Incompatibilities with drugs are also known, e.g. with chlorhexidine acetate.

Sodium stearyl fumarate should be stored in amber glasses with polyethylene screw caps; thanks to it at ambient temperature it is stable up to 3 years. It should be always stored in a well-closed container and in a dry cool place. In manipulation, it is necessary to work in a well-ventilated surroundings and eye protection is recommended.

Use

Sodium stearyl fumarate is used as an alternative to the lubricant magnesium stearate. It also serves as a glidant for tablets and capsules in the concentration of 0.5.-2.0 %. It possesses an identical lubricating efficacy and produces a similar decrease in tablet strength as magnesium stearate. In contrast to magnesium stearate and stearic acid, it is less hydrophobic

and in addition it exerts a less decelerating effect on drug dissolution. It can exist in two polymorphous forms as a small hexagonal plate or needle-shaped crystals. It is just in the form of a plate that it is employed as a tablet lubricant.

Thanks to the fact that it is a nontoxic and non-irritating material, it is employed besides peroral pharmaceutical preparations also in foodstuffs as a direct supplement to foodstuffs for human consumption and also as a stabilising means in various baker's products, processed cereal crops, and flour-thickened products.

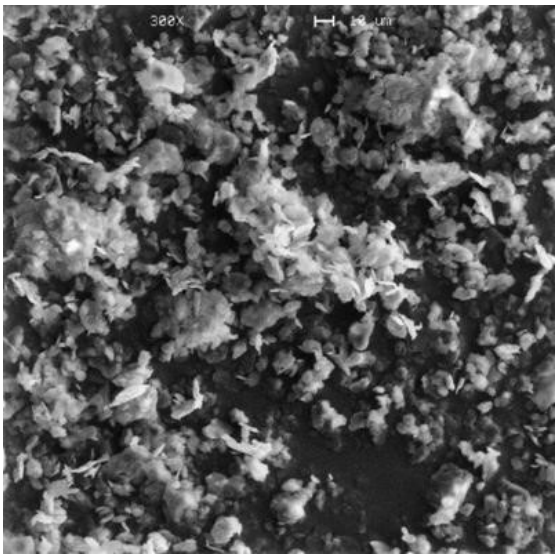

Fig. 2 Sodium stearyl fumarate (enlarged 300x, size 10 μm)

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