MICROCRYSTALLINE CELLULOSE (MCC)

Microcrystalline cellulose is purified, partly depolymerized cellulose prepared by processing of α-cellulose, which is obtained as a pulp from plant tissues by the action of mineral acids under increased temperature and pressure. In the initial material, cellulose fibres are composed of millions of microfibres. Two different areas can be distinguished in microfibres; the paracrystalline area, which is amorphous and flexible material of cellulose chains. The second is the crystalline area, composed of firm bunches of cellulose chains in a firm linear arrangement. Controlled hydrolysis results in removing a large part of the amorphous component, giving way to the aggregates of the more crystalline part of cellulose fibres. After purification by filtration and spray-drying, dry, porous microcrystals with a large surface (130-270 m^2/g) are obtained. The controlled spray and drying conditions may result in different particle size distribution – particle size ranges from 20 to 200 μm. MCC is a white odourless and tasteless crystalline powder composed of porous particles or agglomerates, insoluble in water, diluted acids, and organic solvents; it is slightly soluble in 5% sodium hydroxide.

Microcrystalline cellulose was first marketed in the year 1964 (FMC Corporation) called Avicel® PH in four different degrees of particle size, each with different properties, which enabled selection of a suitable type of Avicel according to the needs. In the year 1992, Avicel® PH was already available in seven types (differing mainly in particle size and humidity content). Avicel can be mixed with a large amount of an active ingredient (up to 70%). The pharmaceutical market offers also other corporate products of MCC, such as, e.g., Emcocel®, Vivapur®, Microcel®, and Comprecel®.

Principal properties of MCC:

Empirical formula: $(C_6H_{10}O_5)_n$, where n=220

Molecular weight: 36 000

Melting point: 260-270_C.

Acidity/alkalinity: pH= 5.0 – 7.0

Humidity content: usually less than 5%

Use according to percentage representation: absorbents (20-90%), filler (20-90%), disintegrant (5-15%).

Dilution potential: the best dilution potential is for the MCC concentration of 20-25%, though sometimes even a lower (10%), or higher (about 50%) one are used.

When comparing the properties of different types of microcrystalline celluloses, density, particle size, largeness of the surface, and humidity content are primarily evaluated, and also the applied properties flowability and compressibility.

Table 1: Comparison of individual tapes of Avicel®PH

Degree Average particle size (μm) Content of moisture Bulk density

Stupeň	Průměrná velikost částic (μm)	Obsah vlhkosti (%)	Sypná hustota (g/cm^3)
PH-101	50	3,0-5,0	0,26-0,31
PH-102	100	3,0-5,0	0,28-0,33
PH-105	20	≤ 5,0	0,20-0,30
PH-102 SCG	150	3,0-5,0	0,28-0,34
PH-200	180	2,0-5,0	0,29-0,36
PH-301	50	3,0-5,0	0,34-0,45
PH-302	100	3,0-5,0	0,35-0,46
PH-103	50	≤ 3	0,26-0,31
PH-113	50	≤ 2	0,27-0,34
PH-112	100	≤ 1,5	0,28-0,34

SCG – speciální hrubý stupeň

SCG – a special rough degree

Scanning electron microphotos show that Avicel® PH 101 possesses a rod-like structure, whereas Avicel® PH 102 is formed by a mixture of primary particles and agglomerates. Primary particles are composed of little fibres of the radius of 10-15 nm with a hollow axis of about 2 nm.

Flowability of Avicelu® PH 101 is bad due to a larger or smaller extension of the rod-like form of the particles, bad distribution of particle size and low flow density. Avicel® PH 102 possesses a better flowability in comparison with Avicel® PH 101 because it is a mixture of agglomerates and primary particles. Flowability of Avicel® PH 103 and PH 105 is smaller than of Avicel® PH 101 and was attributed to the differences in the content of humidity or particle size distribution. FMC introduced Avicel® PH 200 with an average of particle size of 200 μm just because of improved flowability (thanks to spherical aggregates and better particle distribution). A disadvantage of large-particle microcrystalline celluloses can be higher sensitivity to an added lubricant and possibly a lower tablet strength. During direct

compression, MCC is exposed to pressure deformation by several mechanisms. At low compression forces, the removal of inner tension is dominated by slightly elastic phase, which was explained by its hollow microfibre structure. At a higher force, there occurs either further deformation, or permanent deformation by nonspecific final shaping (plastic-elastic deformation). Final shaping is an important factor influencing compressibility of microcrystalline cellulose. Plasticity of MCC is increased with increasing compression force, which is accompanied by a decrease in viscoelasticity. If the tablets with microcrystalline cellulose are prepared by moist granulation, there occurs less deformation in comparison with the tablets prepared by direct compression. A decrease in tablet strength by increasing the rate of compression is caused by increased porosity of the compressed powder layer. Strong binding properties are due to the hydrogen bonds between hydrogen groups on plastically deformed adjacent cellulose particles. Hydrogen bonds on extremely large areas get into close contacts during plastic deformation. This is the reason for very good compressibility of MCC, better than in any other directly compressible dry binder. Exceptionally good binding properties of microcrystalline cellulose are reflected in its extremely high binding index, whereas the index of fragile break is extremely low. Compressibility of MCC depends on humidity content, mostly being about 5%, and majority of water is inside the porous structure. During plastic deformation, humidity inside the pores should act as an inner lubricant and facilitate gliding in the individual microcrystals. Compressibility is decreased with decreased humidity. The strongest compacts are produced with the humidity content of about 7.3%. Tendency to capping is decreased by increasing humidity from 3.2% to 6.1%. Particle size of MCC exerts only small influence on compressibility. Maximal compressibility was found in the particles of the sizes from 80 to 100 μm.

Due to the plastic behaviour, celluloses are sensitive to mixing with lubricants. Alternative lubricants, such as hardened vegetable oil (Lubritab®) or sodium stearyl fumarate (Pruv®), exert, in the case of celluloses, much smaller effect on tablet strength than magnesium stearate. MCC also possesses the properties of a lubricant and a disintegrant. For example, a mixture of up to 40% of spray-dried lactose can be compressed without an added lubricant. Disintegration of the tablet with MCC is attributed to permeation of water into the matrices of hydrophilic tablets by means of pores and subsequent impairment of hydrogen bonds. Penetration measurements show that tablets of microcrystalline cellulose show extremely rapid permeation of water. Absorbed humidity causes impairment of the hydrogen and thus a decrease in tablet strength.

With regard to high costs, bad flowability and low flow density, MCC is not employed only as the basic dry binder in tablets, but it is used after mixing with a cheap filler of good flowability, such as α-lactose monohydrate or calcium phosphate dihydrate. Recent papers show that mixtures of MCC with α-lactose monohydrate in the form of spray-dried lactose or agglomerated lactose can be compressed without problems on a high-speed rotation press.

MCC is one of the most widely used dry binders in direct compression. Thanks to very good binding properties and high stability it is a popular dry binder. It can be used as a filler in tablets prepared by moist granulation, a filler for capsules, a lubricant, and a disintegrant. It possesses high dilution potential in directly compressible formulations.

Silicified microcrystalline cellulose – Prosolv SMCC

Silicified microcrystalline cellulose is a relatively new highly functional pharmaceutical excipient. It was produced aiming to eliminate some shortages of commonly known microcrystalline cellulose. It is employed as a filler for the production of tablets and capsules. Silicified microcrystalline cellulose is a combination of a dry binder and a glidant, it is so-called a mixed dry binder. It is manufactured by co-processing of 98 % of microcrystalline cellulose with 2 % of colloidal silicon oxide.

Properties:

pH: 5.0-7.5

Density: 1.58 g/cm^3

Flow density: 0.31 g/cm^3

Tapping density: 0.39 g/cm^3

Melting point: 260-270 ºC

Humidity content: usually smaller than 6 %

Particle size distribution: 20-200 μm

Solubility: practically insoluble in water, diluted acids, and most organic solutions, partly soluble on a 5% solution of sodium hydroxide.

Silicified microcrystalline cellulose is relatively stable, if the storage conditions are kept. It is produced by spay-drying of a suspension of microcrystalline cellulose and colloidal silicon oxide, so the dry product contains 2 % of colloidal silicon oxide. Colloidal silicon oxide appears physically bound on the surface and inside the mixture there are particles of silicified microcrystalline cellulose. Extensive studies employing various spectroscopic method have not demonstrated any form of chemical interaction.

Advantages of silicified microcrystalline cellulose

Silicified microcrystalline cellulose is a highly functional excipient. It possesses the ability to markedly improve effectivity of the use of costs, time, and subsequently to improve the quality of the solid dosage form. In contrast to other excipients, it has high inner functionality, high compressibility, good flowability, and it also functions as a good lubricant. In the incorporation of an active ingredient it provides good content uniformity of tablets.

Technology of Prosolv®

Silicified microcrystalline cellulose is manufactured by JRS Pharma (Germany) using the trade mark Prosolv® SMCC. Prosolv® SMCC is a patented technology, which produces a portfolio of highly functional excipients. It is a synergic process, which processes excipients such as microcrystalline cellulose and colloidal silicon oxide. In this combination of two excipients, colloidal silicon oxide is added and dispersed in an aqueous suspension of microcrystalline cellulose and it is dried together. Then there originates a perfect mixture known as Prosolv® SMCC (silicified microcrystalline cellulose). Total analysis has demonstrated that Prosolv® SMCC does not contain any other components or covalent bonds. Colloidal silicon oxide simply adheres to the surface of cellulose polymer and silicification takes place. Nevertheless, in some cases it was detected even in the inner areas of particles of silicified microcrystalline cellulose. Some of the internally located silicon oxide is present as a result of silicification or aggregation of particles. Silicification thus changes surface properties of microcrystalline cellulose. It thus may influence, e.g., the strength of the interphase interaction with magnesium stearate due to a competitive inhibition of the binding sites for stearate, thus decreasing the sensitivity to added lubricant. Colloidal silicon oxide is considerably dispersed and uniformly distributed in whole cellulose, which is one of the main advantages of Prosolv®. Greater silicification enlarges also the surface. As the result, Prosolv possesses a four-times larger surface than microcrystalline cellulose. Thanks to it, Prosolv possesses better flowability, compressibility, uniformity of the content of the active ingredient, and stability of the formulation. Two principal size degrees of Prosolv are Prosolv® SMCC 50 and Prosolv® SMCC 90.

References:

1. BOLHUIS, G. K., DE WAARD, H.: Compaction properties of directly compressible materials. In: CELIK, M., ed., *Pharmaceutical powder compaction technology*. USA: InformaHealthcare, 2011. 2nd Ed., 8, p. 143-204. ISBN: 978-1-4200-8917-2.

2. NACHAEGARI, S. K., BANSAL, A. K. Coprocessed excipients for solid dosage forms. *Pharm. Technol*., January 2004, vol. 28, p. 112-122.
3. ALJABERI, A., CHATTERJI, A., SHAH, N.H. et. al. Functional performance of silicified microcrystalline cellulose versus microcrystalline cellulose: a case study. Drug Dev. Ind. Pharm., September 2009, vol. 35, no. 9, p. 1066-1071.
4. STEELE, D. F., TOBYN, M., EDGE, S. et. al. Physicochemical and mechanical evaluation of a novel high density grade of silicified microcrystalline cellulose. Drug Dev. Ind. Pharm., January 2004, vol. 30, no. 1, p. 103-109.
5. TOBYN, M. J., MCCARTHY, G. P., STANIFORTH, J. N. et. al. Physicochemical comparison between microcrystalline cellulose and silicified microcrystalline cellulose. *Int. J. Pharm.*, July 1998, vol. 169, no. 2, p. 183-194.
6. MUŽÍKOVÁ, J., NOVÁKOVÁ, P. A study of the properties of compacts from silicified microcrystalline cellulose. Drug Dev. Ind. Pharm., July 2007, vol. 33, no. 7, p. 775-781.