The Particle Design of Cellulose and the Other Excipients for a Directly Compressible Filler-Binder

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Abstract

Cellulose and saccharide are commonly used filler-binder. This summary refer to the technology for high performance filler-binder of direct compression, using these two materials. In case of saccharide filler-binder, spray dry technology and size controlling of primary particle were the key technology. In case of cellulose filler-binder, two different approaches were made. One was co-processing approach and the other was particle shape controlling approach. Some applications using high performance filler-binder were also introduced.

Keywords: filler-binder, direct compression, microcrystalline cellulose, compactibility, lactose, high performance

Introduction

It is well known that the majority of pharmaceuticals in the market are oral solid dosage form. It is said that the oral solid dosage form will continue to be the mainstream of the pharmaceutical formulations in the future and tablet is the major formulation within the oral solid dosage form. Tabletting seems grownup technology, but there still remain the unknown factors of the technology and there are many points which should be improved. Tablets consist of a lot of pharmaceutical excipients and active ingredients. Compactibility is one of the most important functions within the various functions of pharmaceutical excipients.

There are many substances which describe the function of high compactibility within the pharmaceutical excipients. These materials are divided into two categories: a saccharide group and a microcrystalline cellulose group. In this paper, I have summed up the technology for the high-compactibility excipients from the viewpoint of particle design, mainly focused on the microcrystalline cellulose which considered as the most efficient ingredient for compaction.

1.1 High-compactibility saccharide

1.1.1 High compactibility lactose

Lactose is one of the most commonly used pharmaceutical excipients. It is known that the compactibility of lactose highly depends on the process. Fig. 1 shows the correlation between compactibility and the grade of lactose (offered by DMV Japan). Since beta anhydrous lactose (DCL-22) has different crystal form, we cannot compare it simply in the same system, but we can compare the other lactose which has the same crystal form: alpha lactose mono hydrate (DCL-14, DCL-11, DCL-15 and 100M). Within the alpha lactose mono hydrate group, crystalline lactose 100# (100M) shows the lowest hardness. Then pre-granulated lactose (DCL-15) gives higher hardness of the tablet. Next to the pre-granulated lactose comes the spray-dried lactose. It is well known that pre-granulation or spray drying make goods better compactibility. Both DCL-14 and DCL-11 are made by spray drying methods with the same crystalline form. But the lactose which carried out spray drying of the fine-ground alpha lactose (DCL-14) shows the highest compactibility in the chart. It means that the compactibility of lactose relates to the size of crystal in granules also. Fig. 2 shows the scheme.

Beta anhydrous lactose is made by drum drying followed by grinding. It is said that the sharp particle shape of beta anhydrous lactose particle is the reason of the high-compactibility function. Correctly speaking, beta anhydrous lactose contains about 10% of alpha lactose. The content of alpha lactose depends on the production temperature. Because beta anhydrous lactose consists of a mixture of two crystal phase, and because it dry up before crystal grown up, it consists of small sized beta anhydrous crystal. The small sized crystal might be another possible reason for the high-compactibility of beta anhydrous lactose.
1.1.2 The other high compactibility excipients

Fig. 3 shows high compactibility mannitol and Fig. 4 shows high compactibility sorbitol respectively. Each product seems to be made by spray-drying method. It shows that the primary particle in each photo consists of fine crystal. It seems that the same concept as alpha lactose is also used to attain the high compactibility excipients for each saccharide system.

1.2 Comparison of saccharide system and microcrystalline cellulose system

The high compactibility saccharides, which considered to be made by spray drying, were studied through the brochure. Each of them uses granulated lactose as a comparative example to show the high compactibility of their products.

Since each company uses different unit systems and also they use the different evaluation systems in their brochure, we cannot compare each high compactibility product correctly form the presented data. I converted each unit and plotted it to a graph (Fig. 5) to see rough image of these systems, although unified comparison cannot be made. Even though we cannot compare in detail for each products in Fig. 5, it shows that there is big difference between the microcrystalline cellulose group and the saccharide group. It says that the microcrystalline cellulose group show much higher performance of compactibility compared with the saccharide group).

1.3 Microcrystalline cellulose system

Microcrystalline cellulose is well known high compactibility products. In recent years, high-performance microcrystalline celluloses were lunched as research of the material progressed. I would like to focus on microcrystalline cellulose and to describe the history of invention, the feature of a material, development of the new material, and the characteristic of new materials.

1.3.1 Discovery of microcrystalline cellulose

Microcrystalline cellulose is reported by O.A. Battista and others of the American viscose Co., Ltd. in 1962. At that time, the authority of cel-
Mannitol for direct compression
[Spray dry methods]

Photos were offered by Merck Japan.

Sorbitol for direct compression
[Spray dry methods]

Photos were offered by Merck Japan.

Fig. 3 Mannitol for direct compression.

Fig. 4 Sorbitol for direct compression.

Fig. 5 Compactibility of cellulose and saccharide an overview.
lulose had gathered in the company of viscose rayon: American viscose. When cellulose was hydrolyzed and dried, white powder was made. But they did not know how to use it. They try to use it to diet food etc. Just then a researcher of SmithKline Corp. was studying direct compression technology. He heard of this new white powder and tried to use it to direct compression. It turned out to be the best matched material for direct compression.

As it was often heard in a success story, the microcrystalline cellulose was not aimed to develop for the direct compression.

1.3.2 Microcrystalline cellulose
I would like to explain microcrystalline cellulose a little more in detail. A cellulose molecule has the structure in which the glucose ring chained to make a straight line. Many glucose ring chain ran in parallel, formed the hydrogen bond between molecules into next chain, and became bunch-like structure. This is a crystal of microcrystalline cellulose. These cellulose crystal structures exist in natural cellulose, and make a repetition unit (micro crystalline) with constant size of bunch and length. Micro crystallines are connected to form the long fiber (micro fibril). Cotton is the common example of the cellulose fiber usually seen in which cellulose micro fibril gathered. Cellulose micro fibril looks the similar image as the train (micro crystallite portion) which was connected many cars. The connection part of micro crystallite and micro crystallite and the crevice between micro fibril and micro fibril are roughly combined by the polysaccharide such as free cellulose which is not making crystalline, and or mannose and or xylose. It is the so-called amorphous portion of cellulose. If acid hydrolysis of the cellulose is carried out, acid will penetrate into the amorphous portion, and then hydrolysis will take place in this portion. But as acid cannot penetrate into the inside of micro crystallite, it remains micro crystalline in the cellulose structure. This is microcrystalline cellulose. In the electron microscopic picture of microcrystalline cellulose, willow leave-like micro crystallite is observed on the surface (photo. 1). It is said that microcrystalline cellulose works as a dry binder of tablet that it will be easy to carry out plastic deformation if compression force is received for such a structure.

1.4 Development of the high compactibility tablet binder: SMCC (Silycated Microcrystalline Cellulose)
When we use the microcrystalline cellulose for wet granulation methods, we often experience the low activity of microcrystalline cellulose as a tablet binder. It is said that this phenomena is caused by the horning of the microcrystalline cellulose. If microcrystalline cellulose soaked water then dried, water between the micro crystallite of cellulose make liquid bridge construction between micro crystallite particles at the first stage of drying, and then the liquid bridge let the micro crystallite particles attach tightly each other, making the hydrogen bond between particles, along with drying. Finally a horn like hard cellulose block is produced. This is called horning. Once horning is occurred, the hard particles of cellulose will not carry out plastic deformation when it receives compression force: reduced compactibility. If we adjust the water content precisely or by adding ethanol during wet granulation to avoid hydrogen bond formation, horning does not take place. But the controlling method is very delicate and troublesome work. SMCC was developed to prevent the horning.

When SMCC was used for the direct compression methods, it gave higher hardness of the tablet than the tablet from microcrystalline cellulose. SMCC consists of about 2% of colloidal silica and 98% of microcrystalline cellulose. SMCC is made by mixing these two materials in process, so that silicon particulates are distributed over the surface of microcrystalline cellulose particle then dried. The function of SMCC depends on the way of in-process mixing. The function of high compactibility cannot be obtained only by mixing the two kinds of composing powder products. Such product as SMCC is called “co-processed products,” which gets the special function by the synergistic effect of in-process mixing. Sherwood said that by the in process mixing, the fine particulates of colloidal silica covered on the surface of mi-
crocrystalline cellulose, and this construction is fixed by drying. He said that this construction prevent the horning of microcrystalline cellulose, caused by liquid bridge formation.

The two types of microcrystalline cellulose mixture: a simple mixture of microcrystalline cellulose and colloidal silica, and a co-processed mixture of microcrystalline cellulose and colloidal silica (PROSOLV SMCC90: trade name of JRS Pharma) is compared in Fig. 6. The co-processed mixture of microcrystalline cellulose and a colloidal silica (PROSOLV SMCC90) shows the higher compactibility in this chart, which is not obtained in simple mixture. When microcrystalline cellulose (VVAPUR MCC102: trade name of JRS Pharma) and PRPSOLV SMCC90 are compared, it turns out that PROSOLV SMCC90 gives higher compactibility compared with the compactibility of microcrystalline cellulose (VVAPUR MCC102).

Fig. 6
Compactibility of 3 types of dry binders (SMCC/physical Mixture/MCC).

SMCC is supplied by JRS Pharma under the trade name of “PROSOLV SMCC.” There are three grades which has different particle size and bulk density.

1.5 High compactibility microcrystalline cellulose by particle shape control methods

As I mentioned above, composite is one resolution to get high compactibility microcrystalline cellulose. Asahi-kasei Chemicals Ltd. developed another method to get high compactibility microcrystalline cellulose. That is to control the particle shape of microcrystalline cellulose. Dr. Obae explains that the compactibility of microcrystalline cellulose is related to the aspect ratio of particles in the microcrystalline cellulose powder. If the particles in microcrystalline cellulose powder excel in the direction of a long axis, it is supposed to make an oriented structure by compression force, causing the compression pressure transmits to an inside of the tablet effectively, together with tangling of fibrous particles to make hard tablet. The high compactibility microcrystalline cellulose product developed by this concept was named Ceolus KG-802 (trade name of Asahi-kasei Chemicals). The performance of Ceolus KG-802 against Ceolus PH-101 (trade name of Asahi-kasei Chemicals): the standard type of microcrystalline cellulose is given Fig. 7.

The particle shape of Ceolus PH-101 is given in Photo. 2 and the particle shape of Ceolus KG-802; the high compactibility microcrystalline cellulose is given in Photo. 3. Ceolus KG-802 consists of longer particles than the particles of Ceolus PH-101. Dr. Obae studied the mechanism of Ceolus KG-802 by fractionating powder and studied the difference between Ceolus KG and Ceolus PH. It is showed in Fig. 8. It shows that Ceolus KG, which has long axis of particle, attained high hardness of tablet for each
Fig. 9 shows an image diagram of each particle in die when KG-802 and PH-101 receives compression force. When compressed, the particles of KG-802, which has larger aspect ratio (L/D) than PH-101, oriented, tangled and make a hard tablet, but the particle of PH-101, which has smaller aspect ratio (L/D), little oriented, which prevent the transmittance of compression pressure, make medium hardness of tablet.

Photo. 2 Ceolus PH-101: Standard Grade.

Photo. 3 Ceolus KG-802: High Compactibility grade.

Photo. 4 Ceolus KG-802: High Compactibility grade.

(Offered by Asahi-Kasei Chemicals)

Fig. 7 Performance of Ceolus KG-802.
(Offered by Asahi-Kasei Chemicals)

Fig. 8 Relationship between logT and L/D.
T; hardness of tablet, L/D; average length/diameter ratio of particles, PH grade: the standard grade, and KG grade: the high compactibility grade, were sieved to fractionated to four particle size. Compactibility of each fraction was studied for the average L/D of particles in each fraction. Where:
PH grade/ P1=0.41-0.43: open circle, P2=0.52-0.54: open triangle, P3=0.61-0.65: open square, P4=0.68-0.74: open diamond
KG grade/ P1=0.41-0.43: closed circle, P2=0.52-0.54: closed triangle, P3=0.61-0.65: closed square, P4=0.68-0.74: closed diamond

(Offered by Asahi-Kasei Chemicals)

Fig. 9 Image diagram of the compaction mechanism of Ceolus KG-802.
ity grade, transmit the compression force effectively to the tablet to make the tablet efficiently and precisely at compaction, compared with Ceolus PH-101.

In addition to the compatibility, particle shape of microcrystalline cellulose influences the other powder properties of microcrystalline cellulose. Fig. 12 shows the relation between the compactability and the powder properties for various microcrystalline celluloses. Ceolus KG-802 is bulkier than standard grade, and it is relatively poor flowability of powder. For this reason, Ceolus KG-802 seems to be rejected from the dry binders for high-speed tabletting, but in the case of the mixed powder of an actual formulation, it is not always true. Ozeki reported that a formulation with Ceolus KG 802 is suitable for high-speed tabletting rather than the formulation with standard grade. It means that the powder suitable for high-speed tabletting depends not always on the properties of each component powder but on the properties of formulated powder mixture. Fig. 13 shows the tablet weight variation under the tabletting condition of 8mm phi and 180mg tablet with the formulation 70% of the lactose (Super-Tab/ DMV International) and 30% of microcrystalline cellulose for direct compression. It says that the formulation with Ceolus KG 802 which has angles of repose 49 degree was stabilized at high speed tabletting from the formulation with PH-102 which has angles of repose 42 degree, and the formulation with PH-302 which has angles of repose 38 degree.

1.6 A super-high compactibility microcrystalline cellulose

Ceolus KG-1000 which exceed Ceolus KG-802 are launched from Asahi Chemical Chemicals in recent years. The concept of Ceolus KG-1000 is the same as that of KG-802, which controlled the aspect ratio of particles in the powder. Photo. 4 shows the difference of particle shape between various microcrystalline cellulose and Ceolus KG-1000. It shows that the L/D value of particles in Ceolus KG is much larger than Ceolus KG-802.

Fig. 14 shows compatibility of various microcrystalline cellulose grades. The number in the figure shows the contents (%) of microcrystalline cellulose in each formulation. The remainder is the spray-dry-
Sealing lactose (Super-Tab/DMV International). A rotary tableting machine with 8mm phi punch at 53rpm to make 180mg tablet are used. Ceolus PH-102 is the standard grade which has same compactibility as Ceolus PH-101. In this chart, Ceolus KG-1000 of 10% gives the same tablet hardness as the Ceolus PH-102 of 30%. Ceolus KG-1000 of 20% gives the same effect as Ceolus KG-802 of 30% in this chart.

1.7 Applications for the high compactibility microcrystalline cellulose

The high compactibility microcrystalline cellulose sometimes makes the difficult application possible, which could not be attained in the past. Several examples of these applications are shown below.

1.7.1 Applications for the direct compression of enzyme

Enzyme is one of the delicate active pharmaceutical ingredients, which is easy to lose its enzymatic activity by handling. It is known if we make alpha amylase tablet by direct compression methods, alpha amylase lose enzymatic activity by the compression force during tabletting. Since Ceolus KG-802 require relatively lower tabletting force to get sufficient tablet hardness, when we applied Ceolus KG-802 to the formulation of enzyme, it will keep the enzymatic activity during direct compression. Fig. 15 shows the enzymatic activity of alpha amylase which remained in the tablet. The experimental method of Fig. 15 is shown in Fig. 16. The enzymatic activity of alpha amylase in the formulation with PH-101 drop to 80% of the original activity, at tablet hardness of 50N, which is the limit hardness of tablet for practical use, on the other hand, in the formulation with Ceolus KG-802, enzymatic activity maintained to 95% of the original activity for the same tablet hardness.
1.7.2 Direct compression of the tablet with high content of active ingredients

Generally speaking, the tablet including large amount of active ingredients is difficult to apply direct compression methods. Because of that wet granulation methods is often used for these formulation. By using high compactibility microcrystalline cellulose, people can chose direct compression methods even in the case of high content of active ingredient.

Fig. 18 shows the properties of the tablets obtained by direct compression including various microcrystalline celluloses in the model formulation with large amount of ascorbic acid. In the model formulation of 80% ascorbic acid contents, we could get enough hardness of the tablet for practical use by direct compression, by formulating Ceolus KG-802.

1.7.3 Direct compression of active ingredients with oily physical properties

The formulation which includes the active ingredients with oily physical properties is difficult to make the tablet with enough hardness by direct compression methods. When we make tablet using the powder with oily physical properties, we require the excipients in the formulation not only the function of compactibility but also the function of oozing out the oily ingredient. Since Ceolus KG-1000 is bulky powder, it can absorb the oily active ingredients oozing out during tableting, and at the same time, it can bind the mixed powder as the highest performance tableting agent. For this reason, Ceolus KG-1000 is one of the suitable excipients for the direct compression tablet with the oily active ingredients. The experimental method is shown in Fig. 18 and the tablet hardness and the frying rate of the tablet for the oily active ingredient is shown in Fig. 19. In this formulation system, only the formulation with KG-1000 system attains the hardness of 50N and low frying rate, showing it can be used for the practical application in the market.

1.8 Final Comments

In this summery, I referred to the high compactibility tableting agent, the mechanism of its function, and several applications of these materials, focusing on the microcrystalline cellulose, which is known to the highest compactibility excipients. As far as I
know, the excipients which show the highest compaction performance is Ceolus KG-1000 at present. In the tabletting formulation, the balance of mixed powder (a particle size, particle size distribution, particle shape, chemical properties of the particle, etc.) is critical. Therefore, a high compactibility tabletting agent is not simply evaluated by only compatibility. It is important to employ the characteristic of each material efficiently and it is important also to use properly according to the purpose of its use. In the actual formulation, it often raises difficult problems everywhere. I hope that the high performance tabletting agent introduced in this report may serve as effective solution in such a case. It is well-known that the high compactibility tabletting agent solved the film braking problem of the granule contain tablet. The high compactibility tabletting agent is also applicable for the sustained release drug, orally disintegrating

Fig. 17 Tablet with high Ascorbic acid contents by direct compression.

Formulation/ ascorbic acid: 80%, calcium silicate: 3%, MCC: 15%, croscarmellose: 2%, Magnesium stearate 3 external%. (MCC = microcrystalline cellulose)

Rotary tabletting machine at 50rpm with 12 punches. 12mm diameter, 600mg tablet. (Offered by Asahi-Kasei Chemicals)

Tabletting methods for the formulation including oily API.

Fig. 18 Tableting methods for the formulation including oily API.

| VE prep. | MCC | SD lactose | PCS | MAS |
|----------|-----|------------|-----|-----|
| 10%      | 20% or 0% | 47% or 67% | 20% | 3 w t. % |

To opheral Acetate 50 w t.%
Colloidal Silica 50 w t.%

MCC: Ceolus® KG-1000, KG-802, PH-102

SD lactose: SUPER-TAB

PCS: Pregeratinized starch

MAS: MgAlminometasilicate

(Offered by Asahi-Kasei Chemicals)
tablet in the mouth, etc. It seems that high compactibility excipients have wide range of applications. I am pleased if this summary stands on your work.

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**Author’s short biography**

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Graduated agricultural chemistry of Kyusyu University in 1971 and joined Asahi Chemical Industry Co., Ltd. Engaged to food and pharmaceutical excipient business, mainly microcrystalline cellulose, as business unit manager of R&D, plant manager and general manger of quality assurance. Also was experienced sales & marketing as regional director of South East Asia. Retired under the age clause. As a member of Japan pharmaceutical Excipients Council (JPEC), was experienced the chairman of International Harmonization Committee of JPEC, the chairman of Guideline Committee of JPEC, the chairman of GMP Committee of JPEC. Also experienced a member of the Pharmaceutical Excipients Committee of PMDA: A branch committee of the Japanese Pharmacopoeia Investigation Committee of NHWL. Currently he is the director of “KNOWKATSU” and the consultant of “Inter-Pharma Express Inc.”