CHAPTER II

GENERAL BACKGROUND

Since processing steps of direct compression technique are only mixing and tabletting the blended powder, fewer unit operations are required. This leads to short processing time and less energy consumption. The advantages and disadvantages of this process are listed in Table 2-1 (Jivaraj, Martini, and Thomson, 2000). Because the granulation step that enhances flow and compressibility properties of the powder is omitted, the directly compressible diluent (DC Diluent) must possess these properties. Moreover, the following requirement properties should be included.

1. Compactibility and compressibility : " Compactibility is defined as the ability of the powdered material to be compressed into a tablet of specified strength. Compressibility is the ability of a powder to decrease its volume under pressure" (Leuenberger, 1982). The compression force used should not be so high to give a reasonable hardness.
2. Flowability : This properties relate to many factors, one is the shape, size, and particle size distribution of the particles. In general, the particles should be in spherical form for reducing the friction force between the particles to enhance their flowability.
3. Has disintegration properties
4. High dilution potential
5. Physicological inert, no reaction with drug or other excipients
6. Lubricant insensitivity
7. Reworkability
8. Good stability
9. No odour or taste
10. Reasonable price

Direct compressible excipients can be classified into four groups according to their disintegration property and flowability (Jivaraj, Martini, and Thomson, 2000).

1. Poor flow materials that have disintegration properties e. g. MCC (Avicel®) and directly compressible starch (Starch® 1500)
2. Free flowing materials which do not disintegrate, such as dibasic calcium phosphate dihydrate
3. Free flowing materials that disintegrate by dissolution e. g. lactose, mannitol, and maltose
4. Coprocessed excipients or composite particles (Ohno and Ikeda, 1986; Takeuchi et al., 1999) which are combined excipients by suitable processes. The obtained excipients have the combined synergistic manner and more beneficial than physical mixtures. e.g. silicified MCC (Prosolv®) ; $CaSO_4$ and MCC (Cel –O– Cal®) ; lactose, PVP, and crospovidone (Ludipress®) ; lactose and cellulose (Cellactose®) ; etc.

Table 2-1 Advantages and disadvantages of direct compression process. (Jivaraj, Martini, and Thomson, 2000)

Advantages	Disadvantages
1. "Requires fewer unit operations compared with wet granulation (shorter processing time and lower energy consumption).	1. "Issues with segregation – these can be reduced by matching the particle size and density of the active drug substances with excipients.
2. Fewer stability issues for actives that are sensitive to heat or moisture.	2. In general, the drug content is limited to approximately 30% or approximately 50 mg (Mendes and Roy, 1978).
3. For certain compounds, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation ; for example, norfloxacin.	3. May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin.
4. Fewer excipients may be needed in a direct compression formula".	4. Not suited for poorly flowing drug compounds.
	5. Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing".

As this research is focused in producing of the coprocessed excipient between rice starch and cellulose then only rice starch, cellulose, and coprocessed excipients are discussed.

Rice Starch

Starch, by itself, is not suitable to be used as DC diluents. Bos et al. (1987) investigated various native starches with respect to their properties on compaction. They found that rice starch had the highest compressibility and lower sensitivity to alkaline stearate than other starches. However, rice starch had poor flowability due to the smallest of the starch grain. Many efforts used to improve the flowability and compressibility of this starch as follows.

1. Physical Modification

Physically modified rice starch was produced by spray drying technique. This process produces the agglomerated starch with spherical form that lead to improve flowability and can be used as DC diluent with good disintegration properties.

Mitrevej et al. (1990, 1996) and Hsu-SH et al. (1997) evaluated modified rice starch that is marketed under the trade name of Eratab® compared with other DC diluents (Avicel® PH102, Tablettose®, Starch®1500, and Emcompress®) in term of physical and tabletting properties. They found that the flowability of Eratab® was excellent while those of lactose and MCC were poor. Moreover, Eratab® had more compressibility than other excipients except MCC. Increasing in lubricant concentration lowered the crushing strength of the tablets, however, the tablets properties was still in acceptable range while that of pregelatinized starch (starch®1500) were markedly reduced. Moreover, the disintegration time of Eratab® tablets was independent on the lubricant concentration. When using it in the preparation of drug tablets, it gave the fast and complete dissolution regardless of drug solubility.

Bos et al. (1992) examined spray dried rice starch that is available under the trade name of Primotab®ET in Natherlands (or Eratab®in Thailand) with other DC diluents such as Starch®1500, and Avicel®PH102. It was found that spray dried rice starch gave excellent flowability and disintegration properties. When mixing with

lubricant, the binding properties were sufficient while other starch-based filler was markedly reduced. When it was used as a single diluent or physical combination with other DC diluents at 1 : 1 ratio in making tablets using Oxazepam as a model drug. This modified starch can be used as a unique diluent or in combination with other excipients e.g. α-lactose monohydrate or anhydrous lactose while the combination with MCC should be avoided due to the poor flowability and slow disintegration time of the tablets.

2. Chemical Modification

Timaroon (1993), Timaroon and Kulvanich (1992) investigated the modified rice starch by deproteinization and crosslinking reaction before subjecting to drying by spray drying technique. They found rice starch which deproteinization and crosslinking for 6 hours was a useful product for making tablets by direct compression. Moreover, it gave the tablets with good performance in crushing strength and disintegration properties. Weecharangsan (1995) continued to examine the powder characteristics and tabletting properties of this modified starch compared with the other DC diluents such as Eratab®, Starch®1500, Avicel® PH102, and Emcompress®. They found that this modified starch had the higher compressibility than other DC diluents but inferior to MCC. Tablets containing drugs gave the good results in both of the physical and dissolution properties.

3. Enzymatic Modification

Trubiano and Kasica (1985) prepared compressible starches as a binder for tablets and capsule by acid and/or α-amylase enzyme at a temperature below the starch gelatinization temperature. The level and type of treatment not only depended greatly on the starch source but also related to crystalline and amorphous regions within the granule. Rice starch needed only enzyme treatment to sufficiently alter it granular structure. This modification could be seen by altered, weakened of granules with a less dense interior and ruptured surface. The resulting modified starch was compressible and could be used as a binder for tablets when admixed with a wet granulation binder (e.g. pregelatinized starch) in wet granulation process. And it was also useful as a binder-diluent for capsules in direct compression or dry granulation with good binding and disintegration properties.

From the above researches, it can be summarized the advantages of the modified rice starch as the followings.

1. Excellent flowability
2. Good binding properties and the compressibility can be improved by either physical and/or chemical modification
3. Has self lubrication then tablets with a high concentration of it can be prepared with much lower magnesium stearate concentrations than 0.5%. Moreover, it was less sensitive to mixing with magnesium stearate than the other starch-based filler such as Starch®1500.
4. Has disintegration properties due to a large number of pores between each granules which water can penetrate easily. Furthermore, the disintegration properties is not dependent on compression force used or the mixing time with the lubricant.
5. Suitable for primary amine that is incompatible with lactose due to Maillard reaction
6. Can be used as a unique excipient or with other DC diluents except MCC
7. Cheap and widely available excipient

Cellulose

Naturally occurring cellulose is divided into two groups : the cellulose flocs and microcrystalline cellulose (Czeisler and Perlman, 1991; Shangraw, 1991). Cellulose flocs is produced by mechanical disintegration of compacted pulp sheets and also called powdered cellulose or microfine cellulose. Microcrystalline cellulose (MCC) is prepared by chemical depolymerization (acid hydrolysis) of purified cellulose.

Powdered Cellulose

Powdered cellulose or microfined cellulose is cellulose which prepared by mechanical disintegration. The products are sold under the trade name of Solka-Floc® and Elcema®. Solka-Floc® is introduced firstly as a filler disintegrant. However, it can be used as diluents, binder, and absorption aids. It has many grades with corresponding to its particle size. Due to this material has poor flowability and compressibility then it is not

used as a direct compression diluent. Elcema®(Degussa Co.,) is microfined cellulose which has many grades attributed to its particle size such as Elcema® P050, Elcema® P100, Elcema® F150 and Elcema® G250. The last one is granular grade that possesses sufficient flowability to be used in direct compression. Lamberson and Raynor (1976) compared the tabletting properties of MCC and different grade of powdered cellulose which is called microfined cellulose. It found only Elcema®G250 would form tablets. However, the force used in production of Elcema®G250 tablets was three times higher than that of MCC tablets to produce the same hardness. The low compressibility of microfined cellulose is attributed to a lack of slip planes and dislocations in the cellulose granules. Then it forms a few fresh or clean surfaces during compaction leading to little interparticulate binding. Unlike MCC, this material has poor dilution potential, losing its compressibility rapidly when combined with noncompressible drugs or lubricant.

Microcrystalline Cellulose (MCC)

MCC is aggregated of cellulose microcrystals that is derived from a special grade of α-cellulose by acid hydrolysis. This hydrolysis partially removes the amorphous portions of the cellulose fibers. The level-off degree of polymerization is around 200-300. MCC has many grades with respect to its particle size such as Avicel®PH101 that is small size. Avicel®PH102 is agglomerated product, resulting in higher flowability than the former with no significant decrease in compressibility.

As MCC possesses many good performances such as excellent compressibility at low pressure, high dilution potential, superior disintegration properties, low lubricant requirement therefore it is the best excipient in making tablets by direct compression. However, it has poor flowability and relatively high cost therefore the formulator do not use it as the unique diluent but usually combine it with the other DC diluents to improve the flowability and reduce the cost of the product. The high compressibility of MCC is attributed to hydrogen bonds between adjacent cellulose particles. Moreover, the aggregated form of cellulose microcrystals contain large numbers of dislocation and slip planes which can allow fracture, deformation, and realignment during compression. These are responsible for their large number of clean area which brought in contact and

formed hydrogen bonds during plastic deformation, resulting in the excellent compressibility and the binding ability of less compressible ingredient.

MCC has an extremely low coefficient of friction and therefore has no lubricant requirements itself. However, the lubrication is necessary when the formulation contains drug or other excipients in more than 20%. MCC is also lubricant sensitivity because of it deforms by plastic deformation therefore no new particles or surface area from particles fragmentation under compaction is formed. Because of its high compressibility, the reduction of compact strength is less affected by the small amount of the lubricant. However, the large amount of lubricant used or high intensity of mixing are also affected the hardness of prepared tablets therefore care should be aware in using of it or choosing the mixer in preparing of the formulation.

MCC has good disintegration properties due to the wicking action of the cellulose leading to immediate breaking of the hydrogen bonding when tablets were contacted to the water. Owing to its disintegration property depends on compressional force and it is not act as a primary disintegrant, then it may be used as an auxillary disintegrant in combination with other disintegrants. MCC is water insoluble, the delayed wetting and incomplete dissolution of active ingredient, especially insoluble drug, is obtained because of the physically entrapment or mechanical interlock of drug in the MCC particles, usually in formulation contained more than 80% MCC.

Due to the numerous MCC products are available in the market. The differences in their physical properties and tabletting characteristics exist in various grade and manufacturers. Many researchers have been evaluated the physical properties and tabletting characteristics of MCC products from different lots and sources. They found their physical properties such as particle size, particle density, moisture content, silicification of MCC were all important in affecting the compression and tablet characteristics (Doelker, 1987, 1993; Hwang and Peck, 2001; Williams III, Sriwongjanya and Barron, 1997). The big differences in the tabletting properties among the numerous MCC products are obtained although they comply with compendium specifications. However, the difference between lot to lot variability of the same supplier was

within acceptable limits. Therefore the substitution of the product should be avoided or validated before using.

Coprocessed Excipients

The successful in production of direct compression depends on proper selection of suitable DC diluents which have many properties such as free flowing, highly compressible, soluble, and so on. Due to no single DC diluents is ideal and possess all of the required properties therefore two or more DC diluents are blended together to achieve advantageous properties of each component by coprocessing. Coprocessing is the process of producing new excipient which more than one excipients are combined via one of this process e.g. coprecipitation, spray drying, slugging (Bolhuis and Chowhan, 1996). The resulting excipient could be called coprocessed excipients or composite particles which were found to improve and combine advantageous properties of each excipient by producing superior in physical and tabletting properties to single excipient or physical mixture of the diluents. Coprocessed excipients can be divided in three categories according to the main excipient-type constituent in the powder or the main modified excipient as in the following.

1. Lactose mainly comprised coprocessed excipients e.g. Cellactose®; MicroceLac®; Ludipress®; coprocessed lactose & modified glutinous rice starch; and composite particles of lactose and sodium alginate
2. Cellulose or microcrystalline cellulose mainly comprised coprocessed excipients such as Cel-O-Cal®; coprocessed MCC & $CaCO_3$; Prosolv®; coprocessed MCC & starch or modified starch; coprocessed MCC & β-cyclodextrin
3. Starch mainly comprised coprocessed excipients e.g. coprocessed starch or modified starch & cellulose or microcrystalline cellulose

Cellactose®

Cellactose® is composed of 75% α-lactose monohydrate and 25% cellulose powder (Bauer, Pritzwald-Stegmann, and Luft, 1986). This excipient is rather spherical

form and has microporous within the particles. This material produces good flowability, higher compressibility and short disintegration time. Comparing with other lactose-based filler, with respect to rheological and the fundamental DC properties, Cellactose® produced good flowability than other lactose-based diluents (Tablettose®, Fast-Flo lactose® and anhydrous lactose) but inferior to Ludipress®. In addition, the compression characteristics of Cellactose® are better than other lactose-based diluents (Muñoz-Ruiz et al., 1993). When compared to other DC diluents e.g. lactose and mixture of 75% MCC and 25% dibasic calcium phosphate dihydrate (DCP), with respect to their tabletting property, Cellactose® produced stronger tablets than the other excipients. Moreover, the strength of tablet produced from Cellactose® did not diminish with increasing compression speed as was found in MCC-DCP mixture. This can be attributed to the synergistic effect of consolidation by fragmentation of the lactose component coupled with concomitant plastic deformation of cellulose. Therefore this excipient can be obtained optimum particle bonding (Rubinstein and Garr, 1991). Using this excipient in producing drug tablets, some processing variables e.g. processing method (dry blending, grinding, or spray drying) and formulation (binary or ternary blend, binary is 20% anhydrous theophylline and 80% Cellactose® ; ternary is 20% drug, 60% lactose and 20% MCC) had been examined. The physical properties, flow characteristics and the compressibility of the obtained product was evaluated and showed that the mechanical properties relied on the formulation whereas flow properties and densification depended on the process. Spray drying was found to reduce the differences of the formulation (Viana et al., 2002).

MicroceLac®

New coprocessed filler – binder for direct compression consists of 75% lactose and 25% microcrystalline cellulose produced by spray drying is sold under the trade name of MicroceLac®100. This excipient is the product of Meggle. Michoel, Rombaut and Verhoye (2002) investigates the influence of drug (folic acid) addition on flow behavior, binding properties , interaction and segregation behavior of the drug compared with three different lactoses mixed with MCC. MicroceLac®100 gave superior flow and binding properties to other lactose blend excipients. Moreover, the drug demixing and

segregation was decreased by good adhesion of the drug to the porous surface of excipient. Low dose drug, such as folic acid could be formulated with MicroceLac®100 to give the tablet that conformed to the requirements of content uniformity test.

Ludipress®

Ludipress® is a coprocessed excipient that consisted of three components, a filler, a binder and a disintegrant. The concentrations of its constituents are 93.4% α-lactose monohydrate, 3.2% polyvinylpyrrolidone and 3.4% crospovidone. This excipient exhibits good flow and good compressibility under low pressure. Furthermore, tablets using this material produces tablet with great hardness, low abrasion, and excellent disintegration properties (Lang, 1991). Ludipress® has excellent flowability because this material consists of spherical particles made up of a large number of small crystals with smooth surfaces. The flowability of it is superior to that of physical blend, Cellactose®, and Avicel®PH 200. Moreover, several Ludipress® samples exhibit a good batch to batch uniformity and flow characteristics. From the compaction profile of single excipient, Ludipress® is superior to Tablettose® and physical blend but inferior to Avicel® PH 200 (Rubensdörfer and Schmidt, 1994a). The dilution potential of it, with paracetamol as a model drug, is lower than that of Avicel®PH 102, Elcema®G 250, and Elcema®P 050 (Baykara et al., 1991). When interactive mixing and tabletting with micronized drug, glibenclamide, the disintegration time and dissolution rate show superior results to that of Cellactose® (Rubensdörfer and Schmidt, 1994b). Although this excipient contains a superdisintegrant, the disintegration time is longer than that of other lactose based-filler. This is attributed to the presence of the binder, polyvinylpyrrolidone.

Coprocessed Lactose and Modified Glutinous Rice Starch

Manopaiboon (1997) prepared co-spray dried powders of lactose and sodium carboxymethyl glutinous rice starch having 0.35 degree of substitution for the use as directly compressible diluent. It was found that the better tabletting characteristics was obtained in the formulation with 50% solid content and 3% (on dried basis) of sodium carboxymethyl starch. When comparing this excipients with the other DC diluents e.g. Avicel®PH 102, Emcompress®, Ludipress®, Starch®1500, and Super-Tab®. It exhibited

good flowability and compressibility properties comparable with Ludipress®, better than Emcompress®, Starch®1500, and Super-Tab® , however, lower than Avicel®PH 102. Magnesium stearate had the negative effect on tablet hardness and prolonged disintegration time of this co-spray dried powder. When using it in manufacture of drug tablets, the tablet quality and drug dissolution conformed to the requirement.

Composite Particles of Lactose and Sodium Alginate

A novel composite particles of lactose and sodium alginate was prepared by spray drying technique. This excipient was used as a filler of controlled release matrix tablet. The flowability of this diluent was excellent due to its spherical shape and sharp particle size distribution. Tablets produced by this excipient (with sodium alginate in the composite particles $\leq$ 10%) gave compact with higher tensile strength than that of commercial lactose for direct tabletting and a physical mixture of lactose and sodium alginate. This was attributed to an increased deformability of particles with a decrease in crystallinity of lactose which was dramatically enhanced with the presence of sodium alginate in the particles. The drug release from matrix tablets of this excipient was more prolonged than that of physical mixture because of the improved gel forming property of the sodium alginate (Takeuchi et al. 1998, 1999).

Coprocessed MCC and $CaSO_4$

Coprocessed MCC and $CaSO_4$ or Cel-O-Cal® (FMC corp.) comprised of 70% anhydrous $CaSO_4$ and 30% MCC and produced by spray drying. This material combines the advantages of highly compressible and disintegration properties of MCC and low price of $CaSO_4$. Cal-O-Cal® is significantly more compressible and produces tablets with lower friability than physical mixture of the two excipients. Due to Cal-O-Cal® is composed of two excipients that are water insoluble then care should be taken in using it, especially in the preparation of drug with low water solubility (Shangraw, 1991).

Coprocessed MCC and $CaCO_3$

Mehra, West, and Wiggins (1988) produced and examined the coprocessed MCC and $CaCO_3$ in the ratio 75 : 25 to 35 : 65 at the concentration at least 10% (preferably

20 – 30%) and subsequently spray drying. They found MCC and $CaCO_3$ were intimately associated in the coprocessed particulate product and presented as an agglomerates of the two components which had the particle size less than sieve no. 60 (250 μm) and preferably had an average size in the range of from 20 μm to 150 μm. The powder was free-flowing and suitable to be used as a excipient for vitamins preparations prepared by direct compression. Moreover, this coprocessed excipient was low lubricant sensitivity.

Prosolv®

Due to the dramatic decrease in the compressibility of cellulose was observed after wet granulation. Silicified MCC (SMCC) was developed to overcome this problem. SMCC is a co-processed product which is composed of 98% MCC that is silicified with 2% colloidal silicon dioxide and is marketed under the trade name of Prosolv®SMCC (Mendell Division, Penwest Pharmaceutical Co., Ltd.). This two materials are formed by spray drying process to produce agglomerated microcrystals which are formed as a result of the strong physical association between the two excipients. This excipient is claimed to enhance compressibility of MCC in both direct compression and wet granulation formulation, give better flow properties compared with conventional grades of MCC and a low lubricant sensitivity when blended with magnesium stearate, producing tablets of an acceptable hardness even after prolonged mixing. The advantages of this excipient can be summerized as in the following (Staniforth et al., 1999 ; Sherwood and Becker, 1998)

1. Improves direct compression compressibility and accommodates poorly compactible actives in DC processes
2. Preservation of compressibility in wet granulation, therefore eliminates extra granular addition of MCC in wet granulation processes
3. Increases drug carrying capacity resulting in reduced tablet size
4. Provides excellent disintegration properties
5. Reduces lubricant sensitivity
6. Improves drug content uniformity and material flow in high speed applications

7. Produces harder, less friable tablets
8. Very low strain-rate sensitivity (effect of tabletting speed) therefore increased tabletting production speeds and also increased production capacity

SMCC is available into three grades, SMCC®90M, SMCC®HD90 and SMCC® 50M. They are different in particle size and the density of the powder. SMCC®90M is a large particle grade having particle size distribution equivalent to that of Emcocel®90M and Avicel®PH 102. SMCC®HD90 has the same particle size as in SMCC®90M but the difference is having high density of the powder. These two grades are recommended for use in direct compression. SMCC®50M has the particle size distribution similar to that of Emcocel®50M and Avicel®PH101. This grade is used as excipient for wet granulation and direct compression, either alone or combined with SMCC®90M, to minimize segregation (Sherwood and Becker, 1998).

Coprocessed MCC and β-CD

Tsai et al. (1998) modified physical characteristics of MCC by codrying with β-CD. The slurry form of MCC was blended with β-CD at concentration of 10% to 50%w/w, granulated with water and codried at 60°C for 12 hours or until a constant weight was reached. Codried granules were pulverized, and only the fraction between 61 and 150 μm was evaluated the powder and tabletting properties compared to various grade of MCC and physical mixture. Codrying with β-CD significantly improved the flowability of MCC due to the more rounded shape of particles. Moreover, the compressibility and disintegration properties of tablets produced from the codried products were better than those of MCC alone, physical mixtures, or various grades of MCC. MCC in slurry form was more efficient than the existing MCC products due to the larger amount of water that helped to obtain higher solubility of β-CD and promoted the interaction between β-CD and MCC. This codried product was useful as a excipient for direct compression.

Coprocessed Starch and Cellulose or MCC

Bavitz and Schwartz (1974, 1976) evaluated the physical and compression properties of physical mixture of various DC diluents with MCC at the ratio of 1 : 1 with

product of FMC Corp. which is the coprocessed starch USP (starch USPXVIII implied starch that derived from corn) and MCC at 84 : 16. It was found that physical mixture of MCC and starch USP could not be produced tablets because of its poor flowability while coprocessed excipient gave tablets with acceptable hardness and good disintegration. However, the production of drug tablets that had the required hardness could not be obtained even at the highest compression force. This might be due to the type of starch used, the modification of the starch and/or the ratio of MCC in the coprocessed excipient.

Ohno and Ikeda (1986, 1991) prepared novel coprocessed DC diluents by dispersing hydroxypropyl starch (HPS) and cellulose or MCC in the ratio of 1 : 9 to 6 : 4 in aqueous medium or solution of starch or HPS at concentration of 0.5 – 5% and subsequently drying by spray dryer. The particle size of cellulose used should be reduced its size to obtain 90% of particle size could be passed through a 250-mesh screen or higher. The step of mixing can carried out by dispersed in water in any order to get the final concentration around 10 – 30% solid content. The coprocessed excipient had the physical behavior e.g. flowability and compressibility properties higher than unique HPS or cellulose or physical mixture of HPS and cellulose in the same ratio. When making tablets with rotary-type tabletting machine, coprocessed excipient produced good mold with low disintegration time. Unique HPS or cellulose or mechanical mixture of HPS and cellulose were rough to mold due to their poor flowability and/or low compressibility compared with coprocessed excipient. Moreover, this coprocessed excipient can be used as only single excipient in the preparation or mixed with lactose powder for making tablets. The mixed powder gave smoothly tabletting with hard tablets and low disintegration time.