ABSTRACT

Excipients are no more considered as inert ingredients of formulation, but have a well-defined functional role. The shift in tableting toward direct-compression and high-speed manufacturing has forced the excipient industry to search for new excipients. The search for novel excipient consumes time and investment. Co-processed excipients on the other hand are the result of synergistic properties of existing excipients. Co-processed excipients are a combination of two or more excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change. These excipients have high functionalities as compared to individual excipients like better flow property, compressibility, reduced lubricant sensitivity. Marketed products such as Ludipress, Ludiflash and Prosolv etc. have already proven their worth in the market by reducing the cost of product and number of excipients yet maintaining efficacy of formulation. Such excipients face some limitations due to their quality assessment and reproducibility of results. Regulatory concern is also a prime factor hindering the complete potential of co-processed excipients. International Pharmaceutical Excipients Council (IPEC) is finding a way to get them into official monographs either as mixtures or as single-bodied excipients.

Keywords: Co-processed, IPEC, Particle engineering, Spray drying, Regulatory concern.

INTRODUCTION

The International Pharmaceutical Excipient Council (IPEC) defines excipients as “Substances other than the API which have been appropriately evaluated for safety and are intentionally
included in a drug delivery system (1). For example excipient can aid in the processing of the
drug delivery system during its manufacture; protect, support or enhance stability,
bioavailability or patient acceptability, assist in product identification, or enhance any other
attribute of the overall safety, effectiveness or delivery of the drug during storage or use.
Excipients no longer maintain the initial concept of “inactive support” because of the
influence they have both over biopharmaceutical aspects and technological factors (2, 3).
Most of the ingredients lack some important properties of ideal excipients. Hence
combination excipients can be used which fall into two broad categories: Physical mixtures
and Co-processed excipients. Physical mixtures are simple admixtures of two or more
excipients typically produced by short duration low-shear processing. Various techniques
along with substantial usage of particle engineering and material sciences have been
employed for the introduction of a new class of excipients called as “Co-processed
Excipients” (4, 5). Co-processing is a novel concept of altering excipient functionality by
retaining the favorable attributes, supplementing with newer ones. The International
Pharmaceutical Excipient Council (IPEC) definition of a co-processed excipient is “a
combination of two or more compendial or non-compendial excipients designed to physically
modify their properties in a manner not achievable by simple physical mixing and without
significant chemical change”.

NEED FOR DEVELOPING CO-PROCESSED EXCIPIENTS
Excipients with improved functionality can be obtained by developing new chemical
excipients, new grades of existing materials and new combinations of existing materials. Any
new chemical excipients being developed as excipients must undergo various stages of
regulatory approval aimed at addressing issues of safety and toxicity, which is a lengthy and
costly process. Developing new grades of existing excipients (physicochemical) is the most
successful strategy for the development of new excipients from the past three decades, a
process that has been supported by the introduction of better performance grades of
excipients such as pregelatinized starch, croscarmellose and crospovidone. New combination
of existing excipient is an interesting option for improving excipient functionality because all
formulations contain multiple excipients. Many possible combinations of existing excipients
can be used to achieve the desired set of performance characteristics. However, development
of such combination is a complex process because one excipient may interfere with the
existing functionality of other excipients. Development of single-bodied excipient by
bringing change in the sub-particle level and methodology for development of a new
synergistic combination leads to the phenomenon of co-processed excipients. Co-processing of excipients with moderate supporting data leads to-

- The formation of excipients granulates with superior properties compared with physical mixtures of components or with individual components, especially suitable for direct compression.
- The formation of an ideal filler-binder that can substitute two or more excipients.
- Good compressibility and low weight variation even at short dwell time and at high tableting speed.
- To overcome short comings of existing excipients such as loss of compaction of microcrystalline cellulose upon wet granulation, high moisture sensitivity and poor die filling as a result of agglomeration.
- To address the need of specific patients with diabetes, hypertension and lactose and sorbitol sensitivity.
- Modulation of solubility, permeability and stability of drug molecules.
- To address issues such as disintegration, dissolution and bioavailability.

The continued popularity of solid dosage forms, a narrow pipeline of new chemical excipients and an increasing preference for the direct-compression process creates a significant opportunity for the development of high functionality of excipients(6, 7, 8).

**PRINCIPLE OF CO-PROCESSING BASED ON PARTICLE ENGINEERING**

Particle engineering is a broad concept that involves the modification of particle parameters like shape, size distribution, and simultaneous minor changes(9). Solid substances are characterized by three levels of solid-state. These levels are closely linked to one another, with the changes in one level reflecting in another level. The first level is molecular level which comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. The second level is particle level which comprises of individual particle properties such as shape, size, surface area and porosity. The third level is bulk level which comprises of an ensemble of particles and properties such as flowability, compressibility and dilution potential, which are critical factors in the performance of excipients (10).

**Material characteristics in Co-processing**

Co-processing is generally conducted with one excipient that is plastic which means a permanent change in shape of material due to applied stress and another that is brittle which
means a rapid propagation of crack throughout the material on application of stress.

The co-processing performed with a large amount of brittle material and a small amount of plastic material, as exemplified by Cellactose (Meggle Corp.) in which 75% lactose (brittle material) is co-processed with 25% microcrystalline cellulose (MCC, plastic material), prevents the storage of too much elastic energy during compression, which results in a small amount of stress relaxation and a reduced tendency of capping and lamination. However, examples of the other extreme also exist such as Silicified microcrystalline cellulose (SMCC) has a large amount of MCC (plastic material) and a small amount of silicon dioxide (brittle material). These two situations exemplify the fact that co-processing is generally performed with a combination of materials that have plastic deformation and brittle fragmentation characteristics. A combination of plastic and brittle materials is necessary for improving functionalities such as compressibility, flow properties, strain-rate sensitivity, lubricant sensitivity or sensitivity to moisture, or reduced hornification(2, 3, 4, 11).

METHODS OF CO-PROCESSING

1. Spray drying

Spray drying (fig. 1) is a process of incorporation of dry or solid ingredients during drying, by atomizing active compounds in solution or in the form of suspension (12, 13).

![Fig. 1. Spray drying process](image-url)

*Fig. 1. Spray drying process*

*Advantages of spray drying*

- Possibility to associate non-miscible products in continuous operation
- It allows blending and drying simultaneously soluble and insoluble compounds
- Provides opportunity to fix and protect sensitive active compounds on neutral carrier
• Improves hardness and compressibility
• Enhances machine tableting speed, decreases disintegration time
• Ensures a sturdy formulation with less need of maintaining inventory for various excipients.
• It is cost saving due to elimination of wet granulation production steps, which increases productivity and saves reworking expenses(12)

**Disadvantages**
• Limited versatility in producing particles or structures with the complex morphologies
• Rapid drug release rates often exhibiting a burst effect(2)

Co-processed excipients such as Fast Flo Lactose, Avicel PH, Dipac, Pharmatose DCL40, Ludipress and Microcelac 100 are manufactured by this process. Various grades of MCC manufactured by FMC by co-spray drying are shown in Table 1.

**Table 1. Various grades of Microcrystalline cellulose manufactured by FMC**

<table>
<thead>
<tr>
<th>Name</th>
<th>Ingredients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel HFE</td>
<td>MCC 90, Mannitol 10</td>
</tr>
<tr>
<td>Avicel CE 15</td>
<td>MCC 98, Colloidal silicon dioxide 2</td>
</tr>
<tr>
<td>Avicel DG</td>
<td>MCC 85, Guar 15</td>
</tr>
<tr>
<td>Avicel RC591</td>
<td>MCC 75, Carmellose sodium 11</td>
</tr>
<tr>
<td>Avicel RC581</td>
<td>MCC 89, Carmellose sodium 11</td>
</tr>
<tr>
<td>Avicel CL611</td>
<td>MCC 85, Carmellose sodium 15</td>
</tr>
</tbody>
</table>

**2. Melt extrusion**

Melt extrusion (fig.2) is a process of formation of small beads, pellets from the molten mass which is extruded through extruder.

![Melt extrusion process](image_url)

**Fig. 2. Melt extrusion process**

**Advantages**
• No use of solvent or water
• Fewer processing steps
• Better alternative for poorly soluble drugs
• Less energy required compared with high shear methods
• More uniform dispersion because of intense mixing and agitation

Disadvantages
• Thermal degradation due to use of high temperature can take place
• Flow properties of the materials are essential for processing (14)

Pharmaburst is manufactured by this process.

ADVANTAGES OF CO-PROCESSED EXCIPIENTS

1. Absence of chemical change
Many detailed studies of excipient chemical properties after co processing have proven that these excipients do not show any chemical change. No covalently bonded chemical entity is formed when the individual ingredients are combined to form the co-processed excipients. The absence of the formation of covalent bonds between individual ingredients in the co-processed excipient must be analytically demonstrated over the proposed shelf life or retest period of the co-processed excipient (15).

However, bonds breaking, reorientation, stereochemical environment and the intermolecular forces are responsible for the new shapes that determine the formation of a new material. Compared to their classical relatives, the analytical techniques focus on the characterization of particle size distribution, SEM images, the specific surface area and X-ray diffractogram obtained for these materials. Also the techniques of HPLC, DSC, NMR and FTIR are used in order to aid and control their structural properties. The detailed studies of SMCC with XRD, NMR, IR spectroscopy and Raman spectroscopy have detected no chemical changes (8). This absence of chemical change helps to reduce a company’s regulatory concerns during the development phase (8).

2. Physico-mechanical properties

a. Improved flow property
Controlled optimal particle size and particle-size distribution ensures superior flow properties of co-processed excipients without the need to add glidants (8). The volumetric flow properties of SMCC were studied in comparison with MCC. The particle-size range of SMCC was found to be similar to that of the parent excipients, but the flow of co-processed
excipient was better than the flow of simple physical mixtures due to the spherical shape and even surfaces (17).

Calcium phosphate is mostly unsuitable for direct compression processes but when melt granulated with higher fatty acids exhibited excellent flow properties and compressibility as compared to single excipient(18).

b. Improved compressibility
Co-processed excipients have been used mainly in direct compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler–binder. The compressibility performance of excipients such Cellactose(19), SMCC, and Ludipress have been reported to be superior to the simple physical mixtures of their constituent excipients. Excipients such as MCC lose compressibility upon the addition of water, this phenomenon called as ‘quasihornification’. This property is improved, however, when it is co-processed into SMCC (6).

c. Better dilution potential
Most active drug substances are poorly compressible and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipients(20).

d. Fill weight variation
Co-processed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill-weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near optimal size distribution, causing better flow properties(21). The co-processed excipient made up of calcium phosphate has shown a uniform particle size distribution which leads to lower segregation of particles and hence a lower weight variation as compared to individual excipient (18).

e. Reduced lubricant sensitivity
Most co-processed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. The plastic material provides good bonding
properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network (21).

3. Non physico-mechanical Advantages
Pharmaceutical manufacturers have the option of using a single excipient with multiple functional properties, thereby reducing the number of excipients in inventory. Because they can retain functional advantages while selectively reducing disadvantages, co-processed excipients can be used to develop tailor-made designer excipients. This can be helpful in reducing the time required to develop formulations. Improved organoleptic properties such as those in Avicel CE-15, which is a co-processed excipient of MCC and guar gum were shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability. Although co-processing adds some cost, the overall product cost decreases because of improved functionality and fewer test requirements compared with individual excipients. Co-processed excipients can be used as proprietary combinations and in house formularies can be maintained by pharmaceutical companies, which could help in developing a formulation that is difficult to reproduce and provides benefits in terms of intellectual property rights (22).

4. Co-processed excipients and its advantages in Quality by design (QbD)
The advantages of using high performance excipients in QbD include wider design space, lower number of experiments for design of experiment (DOE) studies and flexibility in manufacturability in a wide variety of specifications to meet the design criteria of the formulators. The wider design space means low probability of rejecting raw material batches and low cost, Process analytical tools (PAT) controls in manufacturing and greater flexibility during production phase.

Design of space for two critical materials attributes- excipient particle size and excipient loss on drying (LOD) - was evaluated for PanExcea MHC300G excipients with that of MCC. It was found that PanExcea MHC300G excipient, D$_{50}$ particle size between 105-135 microns and an LOD between 2.8 to 4.4 produced results that satisfied all critical quality attributes (CQA) of the formulation and tablets containing 63.5% Ibuprofen (D$_{50}$ particle size between 40-70 microns). Formulation of the same active ingredients but with a non-co-processed MCC produced narrower design space specifications compared to a PanExcea MHC300G.
PanExcea MHC300G provides greater formulation flexibility and robustness compared to non-co-processed excipients (23).

LIMITATIONS CO-PROCESSED EXCIPIENTS

1. Fixed ratio
   Major limitation of co-processed excipient mixture is that the ratio of the excipients in a mixture is fixed and in developing a new formulation, a fixed ratio of the excipients may not be an optimum choice for the API and the dose per tablet under development (24).

2. High cost
   Directly compressible co-processed excipients are the specialized products which are produced by patented processes like spray drying, fluid bed drying, roller drying etc. Hence, these products are relatively costly than their respective raw materials from which they are made (24).

3. Dilution potential up to 40%
   Most of the directly compressible co-processed excipients have a capacity to accommodate up to 40% of the poorly compressible active ingredients for example acetaminophen, which would mean that the weight of the final tablet to administer 500 mg of drug would be more than 1.3 grams making the tablet size large and may create difficulty in swallowing.

4. Lack of reworkability for spray dried co-processed excipients
   The original spherical nature of the excipient particles is lost if it is reworked hence loss of its intrinsic property and the increase in disintegration and dissolution profiles (9).

5. Lack of Pharmacopoeial acceptance
   Co-processed adjuvant lacks the official acceptance in pharmacopoeia. For this reason, a combination filler binder will not be accepted by the pharmaceutical industry until it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients.
Table 2. OVERVIEW OF MARKETED CO-PROCESSED EXCIPIENTS

<table>
<thead>
<tr>
<th>Co-Processed Excipients</th>
<th>Manufacturer</th>
<th>Components</th>
<th>Claimed benefits</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludipress®</td>
<td>BASF</td>
<td>Lactose monohydrate-93.4 Kollidon30- 3.2 Kollidon CL-3.4</td>
<td>Low hygroscopicity, good flowability, constant tablet weight</td>
<td>(24)</td>
</tr>
<tr>
<td>Ludiflash®</td>
<td>BASF</td>
<td>Mannitol-90 Kollidon® CL-SF-5 Kollicoat® SR30D- 5</td>
<td>Rapidly disintegrating, mechanically stable tablets</td>
<td>(30)</td>
</tr>
<tr>
<td>Avicel ® CE-15</td>
<td>FMC</td>
<td>MCC- 85 Guar- 15</td>
<td>Less grittiness, improved tablet palatability</td>
<td>(3)</td>
</tr>
<tr>
<td>Pharmatose® CCL40</td>
<td>DMV</td>
<td>B-Lactose- 95 Lactitol- 5</td>
<td>High compressibility, Low lubricant sensitivity</td>
<td>(3)</td>
</tr>
<tr>
<td>Microcelac® 100</td>
<td>Meggle</td>
<td>α-Lactose monohydrate- 75 MCC- 25</td>
<td>Better tablet performance at lower cost</td>
<td>(24)</td>
</tr>
<tr>
<td>StarLac®</td>
<td>Meggle</td>
<td>Lactose- 85 Maize Starch- 15</td>
<td>Good flowability</td>
<td>(3)</td>
</tr>
<tr>
<td>ProSolv®</td>
<td>JRS</td>
<td>MCC- 98 Silicon Dioxide- 2</td>
<td>Better flow, less sensitivity to wet granulation, better tablet hardness</td>
<td>(32)</td>
</tr>
<tr>
<td>Di-Pac®</td>
<td>Domino</td>
<td>Sucrose- 97 Maltodextrin- 3</td>
<td>For direct compression</td>
<td>(3)</td>
</tr>
<tr>
<td>StarCap1500®</td>
<td>Colorcon</td>
<td>Maize Starch, Pregelatinized Starch</td>
<td>Tablet disintegration and dissolution properties that are independent of media pH</td>
<td>(3)</td>
</tr>
<tr>
<td>Xylitab® 200</td>
<td>Danisco</td>
<td>Xylitol- 98 Sodium carboxymethyl cellulose- 2</td>
<td>Directly compressible</td>
<td>(3)</td>
</tr>
<tr>
<td>Pharmaburst™ 500</td>
<td>SPI Pharma</td>
<td>Mannitol, Sorbitol, crospovidone and silica; aspartame; and magnesium stearate</td>
<td>Rapidly disintegrating with superior organoleptic properties</td>
<td>(40)</td>
</tr>
<tr>
<td>PanExcea™ MC200G</td>
<td>J.T. Baker</td>
<td>MCC-89 Hydroxypropylmethyl cellulose-2 Crospovidone- 9</td>
<td>Enable direct compression with high speed tableting</td>
<td>(41)</td>
</tr>
<tr>
<td>LubriTose AN</td>
<td>Kerry biofunctional ingredients</td>
<td>Anhydrous Lactose, GlycerylMonostearate</td>
<td>Eliminate the need for adding a separate lubricant</td>
<td>(42)</td>
</tr>
</tbody>
</table>
1. **Ludipress®**

It is a combination of three excipients namely lactose monohydrate (93.4%) as a carrier, polyvinyl pyrrolidone (3.2% Kollidon 30) as a binder and crospovidone (3.4% Kollidon CL) as a superdisintegrant.

**Advantages of Ludipress**

- Tablet hardness is not affected by tablet press speed
- As it is a single integrated product the storage space required is reduced as compared to three different products
- Similarly the cost for production, analysis and storage are reduced
- Amount of Ludipress used for active ingredients such as Caffeine (125mg), Hydrochlorothiazide (50mg) and Diazepam (10mg) is 374.5, 279.3 and 487.5 respectively (25)
- Ludipress exhibits highest flowability and low hygroscopicity followed by Cellactose, Tablettose, Fast Flo lactose and anhydrous lactose as demonstrated by lower static and dynamic angles of repose (24)

- Baykara et al. reported that the dilution potential of Ludipress® with paracetamol is lower than that of Avicel PH 101, Elcema G250 and Elcema P050 but the binding property of Ludipress was found to be much better than corresponding physical mixture (26).
- Vercammen et al. reported the necessity of lubricant to add in formulation containing lactose monohydrate, PVP, Kollidon CL and had little effect on mixing time with lubricant crushing strength of Ludipress tablets (27). Authors also reported that Ludipress exhibits better tableting characteristics for low dose APIs, and good batch-to-batch uniformity than Cellactose.
- Schmidt and Rubensdorfer reported that the tablets manufactured with Ludipress exhibited optimum disintegration time and compaction pressure independent dissolution of glibenclamide (28).

A typical direct compression formulation of aminophylline tablet containing Ludipress® is shown in Table 3 (29)
### Table 3. Aminophylline tablets (100 mg)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophylline powder</td>
<td>100</td>
</tr>
<tr>
<td>Ludipress®</td>
<td>150</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
<tr>
<td>Aerosil® 200</td>
<td>2</td>
</tr>
</tbody>
</table>

### 2. Ludiflash®

It is a new directly compressible co-processed excipient designed for orally dispersible tablets. It comprises of Mannitol (90%), Kollidon® CL-SF (5%) obtained by granulation with 5% Kollicoat® SR30D, in which mannitol acts as a fast dissolving filler with a sweet taste, Kollidon CL-SF as tablet disintegrant and Kollicoat SR30D as a hydrophobic binder to enhance disintegration. It is not a pure physical blend, but has been co-processed from its three ingredients.

**Advantages of Ludiflash**

- Controlled particle size distribution, particle structure and high bulk density combined to provide good flowability
- This combination provides compact, highly porous and fast disintegrating tablets offering exceptional hardness, friability and smooth mouth feel
- Low hygroscopicity ensures the stability of the active ingredients and of the tablet itself
- It is cost effective and used for preparation of pellets via wet extrusion. Drug loading was possible up to 30% for Ibuprofen and up to 50% for Paracetamol(30)

Sandra Kruse et al. reported that the new excipient Ludiflash® is highly suitable for Risperidone orally dispersible tablets made by direct compression. Tablets were compressed at 50–90MPa since this pressure resulted in rapidly disintegrating, mechanically stable tablets. Tablet characteristics were not influenced by compression speed. During and after disintegration the tablets developed a smooth and pleasant taste. Low-dosed actives do not strongly affect the compression characteristics(30).

A typical formulation of fast-disintegrating famotidine tablets having disintegration time of 27 sec and dissolution of almost 100% after 3 minute is shown in Table 4.
Table 4. Famotidine fast-disintegrating buccal tablets (20 mg)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine</td>
<td>20</td>
</tr>
<tr>
<td>Ludiflash®</td>
<td>267</td>
</tr>
<tr>
<td>Aerosil®</td>
<td>3</td>
</tr>
<tr>
<td>L-Menthol</td>
<td>0.9</td>
</tr>
<tr>
<td>Aspartame</td>
<td>4.5</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td>4.5</td>
</tr>
</tbody>
</table>

3. MicroceLac® 100

It is a co-processed product manufactured by spray drying process. It consists of α-lactose monohydrate (75%) and MCC (25%), also known as Cellactose.

Advantages of MicroceLac 100

- It is designed for direct tableting process which combines filling and binding properties of two excipients as they give synergistic effect
- Used for formulations having high content of active ingredients
- To provide better tablet performance at lower cost
- Various studies have revealed that the lactose: MCC ratio of 75:25 and dextrin as a binder are better than the ratio of 85:15 and hydroxypropyl methylcellulose as a binder (25, 32)
  - Klaus Peter Aufmuth reported that the dilution potential of Cellactose is sufficient to produce medium dosage tablets without the need of further addition of dry binder (31).
  - Belda and Mielck found that due to co-processing Cellactose exhibited enhanced crushing strength compared to the powder mixtures each containing 25% w/w Avicel PH-101 or Elcema P-100 and 75% w/w Tabletose or lactose (100#) (19).

A typical formulation of chlorthalidone tablets have been formulated with Cellactose is shown in Table 5.

Table 5. Chlorthalidone tablets (75 mg)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>75</td>
</tr>
<tr>
<td>Cellactose</td>
<td>220.5</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>1.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
</tr>
</tbody>
</table>
4. Prosolv® SMCC

It is also known as Silicified Microcrystalline cellulose. It consists of microcrystalline cellulose (98%) and fumed colloidal silicon dioxide (2%).

**Advantages of Prosolv**

- It enhances multifunctionality regarding compactibility, flow, blending, lubricant properties and tablet disintegration
- It is available in three different grades Prosolv SMCC 50, SMCC 90, and SMCC HD 90, which differ in average particle size and bulk density
- Prosolv is about 20% more compactable than regular cellulose (32, 33)
  - Fraser et al. reported that silicified microcrystalline cellulose has some improvement in flow but considerably enhanced mechanical properties.
  - Lahdenpaa et al. demonstrated that Silicified microcrystalline cellulose is useful to prepare tablet containing poorly compressible ingredients by direct compression. The silicification affects the moisture sorption and the packing during tapping as well as the particle deformation during tableting. Prosolv showed slight increase in the tensile strength but remarkable increase in the disintegration time of the tablets compared to Avicel (34).

A typical formulation of Chromium Picolinate tablets have been formulated with combination of Prosolv SMCC 50, SMCC 90 shown in Table 6 (35).

**Table 6. Chromium Picolinate tablets**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium Picolinate</td>
<td>4</td>
</tr>
<tr>
<td>Prosolv SMCC 50</td>
<td>15</td>
</tr>
<tr>
<td>Prosolv SMCC 90</td>
<td>135</td>
</tr>
<tr>
<td>PRUV (Sodium stearyl fumarate)</td>
<td>3</td>
</tr>
</tbody>
</table>

5. Avicel CE-15

Solution of MCC (85%) and Guar gum (15%) is spray dried. It provides smoother, creamier mouth feel, less tooth-packing and all this without sacrificing flow or compaction (3).

A typical formulation of Loratadine chewable tablets have been formulated with Avicel CE-15 is shown in Table 7
Table 7. Loratadine chewable tablets (5mg)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loratadine</td>
<td>5</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>356.48</td>
</tr>
<tr>
<td>Mannitol</td>
<td>120</td>
</tr>
<tr>
<td>Avicel CE 15</td>
<td>40</td>
</tr>
<tr>
<td>Maize starch</td>
<td>15</td>
</tr>
<tr>
<td>Citric acid</td>
<td>1.40</td>
</tr>
<tr>
<td>Aspartame</td>
<td>5</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
</tbody>
</table>

➢ K Kathiresan, Vijin P. et al. conclude that Loratadine chewable tablets formulated using Avicel CE 15 and starch paste showed better characteristics of chewable tablets (36).

6. Dipac

It is a free flowing agglomerated product consisting of hundreds of small sucrose crystals (97%) glued together by the highly modified dextrin (3%). Its sweet taste makes it suitable for most directly compressible chewable tablets (3).

Advantages of Dipac

High flowability, low hygroscopicity, sweetness, and non-reactivity with other tablet components.

7. Pharmatose DCL 40

It is a co-processed product consisting of 95% lactose and 5% anhydrous Lactitol. Due to spherical shape and favorable particle size, it exhibits good flowability. It has high dilution potential than other lactose based products due to better binding property. It has very low water uptake at high humidity (3, 37).

8. Avicel RC 591 / CL-611

It is co-processed MCC and sodium carboxymethyl cellulose via co-drying process. Avicel RC (1-2%)/CL (2-3%) dispersible celluloses are used in pharmaceutical suspensions, emulsions, nasal sprays, and creams. Alone MCC and SCMC do not exhibit thixotropy in suspensions. The wide range of thixotropies, viscosities, gel strengths, and dispersion characteristics of Avicel RC/CL provide unparalleled suspension stability and functional versatility (3).
9. Avicel DG

It consists of MCC 75% (plastic) and dibasic calcium phosphate 25% (brittle) co-spray dried and is used in dry granulation processes. Intrgranular roller compacted MCC loses its capacity to undergo plastic deformation during tablet compression. This leads to wear of machine parts and difficulty in achieving hardness. Extragranular Avicel PH 102 also needs to be added for achieving desired tablet hardness. Due to the presence of DCP, Avicel DG improves roller compaction by enabling continuous processing and eliminating extragranular excipients while maintaining fundamental requirements for disintegration and dissolution (3).

10. F-Melt®

F-melt contains mannitol, xylitol, MCC, crospovidone as the main ingredients. It is available in two grades; F-Melt® Type C which contains dibasic calcium phosphate anhydrous and F-Melt® Type M contain Magnesium aluminometasilicate, additionally. Type C is for faster disintegration needs, while Type M has better flow properties and improves the overall quality of tablets. Although both types do not differ significantly in their physical properties, it is necessary to test the suitability of the specific API with both types (38).

A typical formulation of Acetaminophen Orally disintegrating tablets have been formulated with Type M- F-Melt® is shown in Table 8.

**Table 8: Acetaminophen Orally disintegrating tablets**

<table>
<thead>
<tr>
<th>Acetaminophen (wt %)</th>
<th>30.00</th>
<th>40.00</th>
<th>30.00</th>
<th>30.00</th>
<th>40.00</th>
<th>30.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-Melt® Type C</td>
<td>-</td>
<td>-</td>
<td>69.6</td>
<td>59.6</td>
<td>59.6</td>
<td>69.6</td>
</tr>
<tr>
<td>F-Melt® Type M</td>
<td>69.6</td>
<td>59.6</td>
<td>69.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Compression force (kN)</td>
<td>5.4-5.7</td>
<td>5.9-6.4</td>
<td>7.5-8.0</td>
<td>5.5-5.8</td>
<td>8.1-8.7</td>
<td>9.0-9.5</td>
</tr>
<tr>
<td>Tablet hardness (N)</td>
<td>36.4</td>
<td>30.2</td>
<td>59.8</td>
<td>31.7</td>
<td>36.6</td>
<td>49.1</td>
</tr>
<tr>
<td>Disintegration time (Sec.)</td>
<td>20.2</td>
<td>20.8</td>
<td>45.5</td>
<td>14.6</td>
<td>21.5</td>
<td>66.52</td>
</tr>
<tr>
<td>Mouth feel</td>
<td>Very good</td>
<td>Very good</td>
<td>Very good</td>
<td>Very good</td>
<td>Very good</td>
<td>Very good</td>
</tr>
</tbody>
</table>

F-melt exhibits excellent tableting properties and facilitates rapid water-penetration for a fast disintegration time(39).

11. Pharmaburst™ 500

Pharmaburst is a co-processed excipient which consists of mannitol, sorbitol, crospovidone and silica; aspartame; and magnesium stearate. Pharmaburst 500 is a ready to use system
which has been specifically engineered to manufacture robust, rapidly disintegrating ODTs with superior organoleptic. Pharmaburst can be used on standard tableting equipment to formulate tablets with up to 500mg API. Simple dry blending of API, flavor, color and Pharmaburst 500 is needed. It allows rapid disintegration and low adhesion to punches. The Loratidine 10mg ODT manufactured with Pharmaburst™ 500 exhibited suitable hardness, low friability and extremely rapid USP/EP disintegration time (4.9 seconds) and extremely rapid oral disintegration time (7 seconds), indicating the utility of Pharmaburst™ 500 in the manufacture of low-dose ODTs.

12. PanExcea™ MC200G
It consists of MCC 89% (diluent), hydroxypropylmethyl cellulose 2% (binder) and crospovidone 9% (disintegrant) prepared by spray granulation. PanExcea has strong intraparticle bonding bridges between the components which results in a unique structural morphology comprising of open structures or hollow pores. Presence of these pores provides a surface roughness that is the ideal for improved blending with an Active Pharmaceutical Ingredient.

Advantages of PanExcea™ MC200G
- It increases drug loading capability as a result of the novel particle morphology
- It optimized powder flow characteristics and compressibility enable direct compression with high speed tableting to enhance productivity
- It provides desired disintegration times with exceptional tablet hardness

13. Lubritose™ AN / SD / MCC
LubriTose™ combines a lubricant with a compression aid, allowing for the blending of the API, followed by tableting, without a final lubricant blend step. It is based on one of the following widely used compression aids, Anhydrous Lactose, Spray Dried Lactose, and MCC, all of which are co-processed with GlycerylMonostearate as the lubricant. The three products are called LubriTose™ AN (Anhydrous Lactose/GlycerylMonostearate), LubriTose™ SD (Spray Dried Lactose/GlycerylMonostearate) and LubriTose™ MCC (MCC/GlycerylMonostearate).

LubriTose™ SD has the fastest flowability rate of the LubriTose™ systems, creating the capabilities to achieve the highest tablet press speeds. LubriTose™ AN has the fastest dissolution rate and highest degree of moisture stability of the LubriTose™ systems. It is
suitable for use in all direct compression applications and in moisture sensitive formulations due to its anhydrous properties and is particularly effective in providing exceptional content uniformity when tableting high bulk density active ingredients. LubriTose™ MCC is specifically designed for use in direct compression, high speed tableting operations where consistency, production efficiency and cost are essential (42).

**REGULATORY CONCERN**

As excipients are incorporated in the final formulations that also remain in the final product they should have safety concern. For a new excipient to be accepted by regulatory authorities, it is required to demonstrate studies on chronic and acute toxicity, pharmacokinetics, toxicology and reproductive effects, as it is considered a new entity. With the absence of a chemical change during processing and no need to perform a full toxicological assessment, co-processed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory agencies with well-documented toxicological studies. It should be possible to provide data to ‘bridge’ to the safety data of the components. However the bridging assessment needs to be fully justified by demonstrating that the co-processing process does not create a change of regulatory significance.

A very limited number of co-processed excipients are included in pharmacopoeial monographs such as Microcrystalline Cellulose and Carboxymethylcellulose Sodium (USNF) Dispersible Cellulose BP and Compressible Sugar (USNF) (BP).

The individual ingredients used in a co-processed admixture must have USP–NF monographs, or at least monograph proposals published in Pharmacopeial Forum as part of in process revision. A co-processed excipient is typically produced by specialized manufacturing process while submission as a potential NF monograph, information relating to its quality must meet current NF submission requirements. The claimed co-processed excipient is either included in an FDA approved drug application or has a GRAS designation or is under special consideration by the Council of Experts. At least one of the components of the co-processed excipient is capable of being analyzed qualitatively and quantitatively in the co-processed state, i.e., without the use of any specific physical or chemical methods to separate the components of the co-processed excipient before analysis of the individual component(s).
IPEC-Americas Co-processed Excipients Workshop held in 2013 has recognized its aim of developing an IPEC-Americas Co-processed Excipient Guide: It is a Guide that provides advice on how to address technical, safety and regulatory concerns relating to the development and commercialization of co-processed excipients.

For the US market, the excipient manufacturer is strongly advised to submit a Type 4 DMF for the new co-processed excipient. This will simplify any regulatory filings in the US until a USP-NF monograph is issued. If a safety data package is required and available, this should be submitted as a Type 5 DMF. Letters of access will be required for both DMFs (43, 44, 45, 46).

CONCLUSION
The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made “designer excipients” to address specific functionality requirement. Using co-processed excipients in the formulation enhances the design space and widens the ranges for both critical quality attributes and critical process parameters compared to traditional non-co-processed excipients. Highly functional co-processed excipients can help to reduce drug dosages, minimize side effects and therefore make medicines better and safer. The United States Pharmacopoeia (USP) encourages development of monographs for co-processed excipients and IPEC is drafting a guideline to facilitate development and adoption of co-processed excipients.

Now a day’s many excipients are also being co-processed directly with API’s to develop a composition ready for direct compression, such as co-spray drying of acetaminophen, mannitol, erythritol, maltodextrin and a superdisintegrant (Kollidon CL). Co-processed excipients are being developed to aid in targeted drug delivery such as Peptide Dalargin to brain using Polyisobutylcyano acrylate whose surface is being modified with Tween 80. Excipient mixtures or co-processed excipients have yet to find their way into official monographs, which is one of the major obstacles to their success in the marketplace. With recommendations from International Pharmaceutical Excipients Council (IPEC), these products could find their way into official monographs either as mixtures or as single-bodied excipients. Once the obstacles are overcome, the use of co-processed excipients can be expected to increase dramatically.
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