RECENT RESEARCH ON CO-PROCESSED EXCIPIENTS FOR DIRECT COMPRESSION-A REVIEW
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Received: 28 December 2012; Revised: 19 January 2013; Accepted: 30 January 2013; Available online: 5 February 2013

ABSTRACT
In recent years great interest has been shown on direct compression, directly compressible excipients and co-processing in pharmacy industry and research. Direct compression is the process of making tablets without granulation step. Direct compression offers several advantages such as low cost, more suitable for moisture and heat sensitive drugs, faster dissolution rates, improved stability etc. Specially processed and modified excipients are needed for direct compression. Co-processing is one of the most widely explored methods for preparing directly compressible excipients. Literature on direct compression, co-processing, directly compressible excipients and recent research on developing co-processed directly compressible excipients are reviewed in this article.

Keywords: Direct compression; Co-processing; Directly compressible excipients; Recent Research.

INTRODUCTION
Direct compression is the process of tabletting of a blend of ingredients, the compression mix, without a preliminary granulation or aggregation process. The compression mix contains the active pharmaceutical ingredient blended with one or more excipients.1 It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. The use of directly compressible excipients may yield satisfactory tablets for such materials. Although simple in terms of unit processes involved, the direct compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential. Tablets consist of active drugs and excipients, and not one drug substance or excipient possesses all the desired physicomechanical properties required for the development of a robust direct-compression manufacturing process, which can be scaled up from laboratory to production scale smoothly. Most formulations (70–80%) contain excipients at a higher concentration than the active drug. Consequently, the excipients contribute significantly to a formulation’s functionality and processability. In simple terms, the direct-compression process is directly influenced by the properties of the excipients. The physicomechanical properties of excipients shall ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machineability even in high-speed tabletting machinery with reduced dwell times. The majority of the excipients that are currently available fail to live up to these functionality requirements, thus creating the opportunity for the development of new high functionality excipients.

IDEAL REQUIREMENTS OF DIRECTLY COMPRESSIBLE EXCIPIENTS
The directly compressible excipient should be free flowing. Flowability is required in case of high-speed rotary tablet machines, in order to ensure homogenous and rapid flow of powder for uniform die filling. During the short dwell-time (milliseconds), the required amount of powder blend should be transferred into the die cavities with reproducibility of ±5%. Many common manufacturing problems are attributed to incorrect powder flow, including nonuniformity in blending, under or over dosage and inaccurate filling.2 Compressibility is required for satisfactory tabletting, i.e. the mass must remain in the compact form once the compression force is removed. Few excipients can be compressed directly without elastic recovery. Hence, the directly compressible excipients should have good compressibility, i.e. relation between compaction pressure and volume.

Dilution potential can be defined as the amount of an active ingredient that can be satisfactorily compressed into tablets with the given directly compressible excipient. A directly compressible excipient should have high dilution potential so that the final dosage form has a minimum possible weight. The dilution potential is influenced by the compressibility of the active pharmaceutical ingredient. A directly compressible excipient should be capable of being reworked without loss of flow or compressibility. On recompression, the excipient should exhibit satisfactory tabletting characteristics. The excipient should remain unchanged chemically and physically. The directly compressible excipient should not exhibit any physical or chemical change on ageing and should be stable to air, moisture and heat. A directly compressible excipient should have a particle size equivalent to the active
ingredients present in the formulation. The particle size distribution should be consistent from batch to batch. Reproducible particle size distribution is necessary to achieve uniform blending with the active ingredient(s) in order to avoid segregation. It should not accelerate the chemical and/or physical degradation of the API(s) or excipients. It should not interfere with the biological availability of active ingredient/s. It should be compatible with all the excipients present in the formulation. It should be physiologically inert. It should not interfere with the disintegration or dissolution of the active ingredient. It should be colourless and tasteless. It should be relatively cost effective and available in desired time. It should accept colorants uniformly. It should show low lubricant sensitivity. It should show batch-to-batch reproducibility of physical and physico-mechanical properties. It should possess proper mouth fill, which is defined as the feel or the sensation in the mouth, produced when the excipient is used in chewable tablets.

**ADVANTAGES OF DIRECT COMPRESSION**

The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms. Disintegration or dissolution is the rate-limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression. The chances of wear and tear of punches and dies are less. Materials are ‘in process’ for a shorter period of time, resulting in less chance for contamination or cross contamination, and making it easier to meet the requirement of current good manufacturing practices. Due to fewer unit operations, the validation and documentation requirements are reduced. Due to the absence of water in granulation, chance of microbial growth is minimal in tablets prepared by direct compression.

**LIMITATIONS OF DIRECT COMPRESSION**

Direct compression is more prone to segregation due to the difference in density of the API and excipients. The dry state of the material during mixing may induce static charge and lead to segregation. This may lead to the problems like weight variation and content uniformity. Directly compressible excipients are the special products produced by patented spray drying, fluid bed drying, roller drying or co-crystallization. Hence, the products are relatively costly than the respective raw materials. Most of the directly compressible materials can accommodate only 30–40% of the poorly compressible active ingredients like acetaminophen that means the weight of the final tablet to deliver the 500 mg of acetaminophen would be more than 1300 mg. The large tablets may create difficulty in swallowing.

**METHODS OF PREPARING DIRECTLY COMPRESSIBLE EXCIPIENTS**

Directly compressible excipients can be prepared by various methods listed in Table 1. Co-processing is the one of the most widely explored and commercially utilized method for the preparation of directly compressible adjuvants.

**Table 1. Summary of various methods used to prepare directly compressible excipients**

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages and limitations</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical modification</td>
<td>Relatively expensive, Requires toxicological data, Time consuming</td>
<td>Ethylcellulose, Methylcellulose, Hydroxypropylmethylcellulose, and carboxyl methyl cellulose from cellulose, cyclodextrin from starch, lactitol</td>
</tr>
<tr>
<td>Physical modification</td>
<td>Relatively simple and economical, compressibility may alter</td>
<td>Dextrose or Compressible sugar, Sorbitol, α-Lactose monohydrate, Dibasic calcium phosphate</td>
</tr>
<tr>
<td>Grinding and/or sieving</td>
<td>Impart flowability to excipients, Requires stringent control on possible polymorphic conversions and processing conditions</td>
<td>β-Lactose, Dipac</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Spherical shape and uniform size, good flowability, poor reworkability</td>
<td>Spray-dried lactose, Emedex, Fast Flo Lactose, Avicel pH, Karion Instant, TRI-CAFOS S, Advantose 100</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Increased binding properties</td>
<td>Anhydrous α-Lactose</td>
</tr>
</tbody>
</table>

**CO-PROCESSING AS SOURCE OF NEW DIRECTLY COMPRESSIBLE EXCIPIENTS**

Co-processing is a process in which two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. The main aim of co-processing is to obtain a product with added value related to the ratio of its functionality / price.

Co-processing is interesting because the products are physically modified in a special way without altering the chemical structure. A fixed and homogenous distribution for the components is achieved by embedding them within mini granules. Segregation is diminished by adhesion of the actives on the porous particles making process validation and in process control easy and reliable. The randomized embedding of the components in special mini granules minimizes their anisotropic behavior. So, deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. Thus, the use of the co-processed excipient combines the advantages of wet granulation with direct compression. Most important characteristics are binding and blending properties of the co-processed excipients, which must be better than those of a physical mixture of the starting materials. Cost is another factor to be considered in the selection of co-processed product. Examples of co-processed directly compressible excipients are given in Table 2.
**ADVANTAGES OF THE CO-PROCESSED DIRECTLY COMPRESSIBLE EXCIPIENTS**

- Absence of chemical change\textsuperscript{10}
- Improved flow properties\textsuperscript{11}
- Improved compressibility\textsuperscript{12-15}
- Better dilution potential\textsuperscript{16}
- Fewer fill weight variation\textsuperscript{13}

**RECENT RESEARCH ON CO-PROCESSED EXCIPIENTS FOR DIRECT COMPRESSION\textsuperscript{18-26}**

Recent research on development of co-processed excipients for direct compression is summarized in Table 3.

**Table 3. Recent Research on Co-processed Excipients for Direct Compression**

<table>
<thead>
<tr>
<th>S No</th>
<th>Co-processed excipients investigated</th>
<th>Technology / Method used for Co-processing</th>
<th>Drugs studied (category)</th>
<th>Result/Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Crosspovidone-Croscamelllose sodium (1:1, 1:2, 1:3)</td>
<td>Solvent evaporation</td>
<td>Metoclopramide (antiemetic)</td>
<td>Superior in flow and compression characteristics</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>Crosspovidone-Sodium starch granulate (1:1, 1:2, 1:3)</td>
<td>Solvent evaporation</td>
<td>Metoclopramide (antiemetic)</td>
<td>superior in flow and compression characteristics</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Chitosan and Aerosil(1:1)</td>
<td>Co-preparation method</td>
<td>Metoclopramide (antiemetic)</td>
<td>Superior in flow and compression characteristics</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Mannitol Microcrystalline Cellulose pH 101 (1:1, 1:2, 2:1, 2:1, 3:1, 4:1, 1:1, 1:2, 1:2, 1:3 and 1:4)</td>
<td>Spray drying</td>
<td>Glibizide (Anti diabetic)</td>
<td>Improved performance of fast dissolving tablets</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>Physically modified (nitric acid treated) wheat starch and Dicalcium phosphate</td>
<td></td>
<td>Acetaminophen (NSAID)</td>
<td>Improved flow and compressibility characteristics.</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>Lactose and Mannitol (1:1, 1:2, 2:1, 1:3, 3:1, 90, 80 and 70%)</td>
<td>Melt granulation</td>
<td>Acetaminophen (NSAID)</td>
<td>The tablets manufactured showed relatively better disintegration time and in-vitro drug release</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>Dicalcium phosphate and Starch (25:75)</td>
<td></td>
<td>Acetaminophen (NSAID)</td>
<td>Exciipients showed optimum compressibility characteristics and tablets showed fast disintegration</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>Pre gelatinized starch-Microcrystalline Cellulose</td>
<td>Gelatinizing potato starch in presence of MCC</td>
<td>Sulphamethoxazole (Anti bacterial) Paracetamol (Antipyretic) Acelofenac (NSAID)</td>
<td>PGS-MCC co-processed excipient developed in this study was found to be a promising directly compressible vehicle</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>Microcrystalline tapioca starch with Lactose monohydrate- ‘microcrystallar’</td>
<td></td>
<td>Paracetamol (antipyretic) Ascorbic acid (anti scurvic)</td>
<td>Microcrystallar shows improved functionality over direct physical mixture of the primary excipients.</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>Mannitol:Cellulose (50:50, 60:40, 70:30)</td>
<td>Freeze thawing technique</td>
<td>Acelofenac (NSAID) Nimesulide (NSAID) Metformin (antidiabetic)</td>
<td>Flowability, compactability, and dissolution rate were improved profoundly</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>PEG 4000, Gelucire 44/14, Gelucire 50/13, Crosspovidone</td>
<td>Melt granulation agglomeration</td>
<td>Acelofenac (NSAID)</td>
<td>Melt granulation agglomeration may be adopted in preference to spray drying.</td>
<td>34</td>
</tr>
<tr>
<td>Excipient Type</td>
<td>Processing Method</td>
<td>Description</td>
<td>Properties</td>
<td></td>
<td></td>
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<tr>
<td>Microcrystalline cellulose, Silicon dioxide and Crospovidone</td>
<td>Spray drying</td>
<td>Diclofenac sodium (NSAID), Iron polymaltose (Treatment of iron deficiency anaemia), Amoxicillin trihydrate (antibiotic)</td>
<td>The co-processed materials have excellent flow properties, high compressibility, lower disintegration time to tablets and have better binding properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose, Colloidal silicon dioxide and Sodium starch glycolate</td>
<td>Spray drying</td>
<td>Diclofenac sodium (NSAID), Iron polymaltose (Treatment of iron deficiency anaemia), Amoxicillin trihydrate (antibiotic)</td>
<td>The co-processed materials have excellent flow properties, high compressibility, lower disintegration time to tablets and have better binding properties</td>
<td></td>
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<tr>
<td>Directly compressible co-processed sustained release multifunction agent (DCSRA) comprising Povidone K 25: Glycerol behenate</td>
<td>Hot melting</td>
<td>Tramadol HCl (analgesic)</td>
<td>The DCSRA exhibited good flow and compressibility and it served as a retardant, binder and lubricant in Tramadol HCl sustain release tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose with SSL Hydroxypropyl cellulose (1:1, 1:2, 1:3)</td>
<td>Spray drying</td>
<td>Tizanidine Hydrochloride (Centrally acting muscle relaxant)</td>
<td>Formulation showed minimum disintegration time and higher amount of drug release in 1:3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crospovidone: Croscarmellose (1:1, 1:2, 1:3)</td>
<td>Solvent evaporation</td>
<td>Chlorothalidone (Antihypertensive and antidiuretic)</td>
<td>The dissolution rate of chlorothalidone was enhanced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crospovidone: Sodium starch glycolate (3:1)</td>
<td>Solvent evaporation</td>
<td>Celecoxib trihydrate (oral cephalosporin) (NSAID)</td>
<td>Exhibited excellent flow and compression, improved dissolution</td>
<td></td>
<td></td>
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<tr>
<td>Pregelatinized starch-Polyvinyl pyrrolidone</td>
<td>Gelatinizing potato starch in the presence of PVP</td>
<td>Ritonavir, Efavirenz, Stavudine (antiretroviral)</td>
<td>Exhibited excellent to good flow properties</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Direct compression as a process of tablet manufacturing and co-processing for preparing directly compressible excipients are widely accepted in Pharma industry. Though considerable research has been done in recent years in the area of developing directly compressible excipients by co-processing, more intensive investigation are to be undertaken in this area which will result in new technologies and better excipients for tabletting.

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