REVIEW ON NOVEL PHARMACEUTICAL COPROCESSED EXCIPIENTS

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ABSTRACT:
Excipients play an important role in formulating a dosage form. In recent years drug formulation scientists have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufacturing adequately. In addition to this the cost involved in development of new chemical excipients with improved properties is quite high. In response numbers of combination excipients introduced by excipient manufacturers into the commercial market. New combinations of existing excipients are an interesting option for improving excipient functionality now-a-days. Particle engineering of individual excipients and excipient combinations using coprocessing, by virtue of sub particle modifications, has provided an attractive tool for developing high functionality excipients that are suited to modern tablet manufacturing processes. Coprocessed excipients are a combination of two or more excipients designed to physical mixing and without significant chemical change. These Coprocessed excipients have high functionalise compared to individual excipients such as better flow property, compressibility, reduced lubricant sensitivity. All the developed co-processed excipients are enlisted highlighting their multi-functional and beneficial characteristics. Regulatory issues concerned with the development of new excipient as well as coprocessed excipients are also discussed. Such excipients for some limitations due to their quality assessment and reproducibility of result.

KEYWORDS:
Types of excipients, Coprocessed excipients, Method of coprocessing, marketed Coprocessed excipients, multifunctional excipients.

1. INTRODUCTION:
In recent time, excipients are the largest components of any pharmaceutical formulations[1]. The international pharmaceutical excipients council (IPEC) defined excipients as substances other than the API which have been properly evaluated for safety and are purposefully include in drug delivery system.[2] Preserve, support or enhance stability, bioavailability, patient acceptability or performance of technological function. Improve in product identification or enhance any other quality of overall safety, effectiveness [3]

1.1 TYPE OF EXCIPIENTS:
- Single entity excipients.
- Mixtures/blends of multiple excipients.
- Novel excipients or new chemical organization.
- Co-process excipients.

1.1.1 Single entity excipients: It is defined as excipients containing one component which is the primary component called as single entity excipients [2]

1.1.2 Mixture/blends of multiple excipients: Simple physical mixtures of two or compendial /non-compendial excipients by means of low to medium shear process where the individual components are mixed together without significant chemical change.
for solid mixture/ blends the individual excipient remain physically separate at a particulate level [3].

1.1.3 Novel excipients or new chemical entities: It is defined as excipients which are chemically modified to form new/novel excipients, these are generally not listed in FDA inactive ingredient database. The new excipient means any inactive ingredient that are intentionally added to therapeutic and diagnostic products[3].

1.1.4 Co-process excipients: co-process excipients are combination of two or more compendia or non-compendia excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change.(4).many different co-processing methods includes in pharmaceutical formulation development such as spray drying, solvent evaporation, crystallization, melt extrusion and granulation/agglomeration[5]

**Advantages of co-processed excipients:**

- Improving flow properties by controlled optimal particle size and size distribution.
- Improve compressibility ,dilution potential, fill weight variation, flow property, lubricant sensitivity.
- It can be also improving the tablet hardness and decrease disintegration time.[5]

1.2 NEED OF CO-PROCESS EXCIPIENTS:

- The developing acceptance of the direct compression process and required for an ideal filler-binder that can substitute two or more excipients.
- The capability to modulate the solubility, permeability or stability.
- To address the problems of flowability, compressibility and disintegration potential.
- Effective use of existing excipients: the developing popularity of the process for ideal filler binder that can substitute two or more excipients.
- Appreciation of new applications for the economical excipients is a inexpensive and less time involving process as compared to an absolutely new development.
- The number of actual excipients which some of desirable properties appropriate in some formulation.
- As new drugs are being development, their compactibility with the existing excipients.

- Hence co-process excipient will be appropriate to overcome these problems.
- The development and improvements in pharmaceutical formulation process and equipments especially enhance in production rate at low cost.[6]

1.3 The co-processed excipient involve the following steps:[7,27]

1. Recognition the excipient group to be co-processed by carefully study. The material characteristics and functionality required.
2. Select the proportions of various excipients.
3. Evaluate the particle size required for co-processing, this is mostly important when one of the components is processed in a dispersed phase post processing, the particle size of the latter depends on its initial particle size.
4. Selecting appropriate drying process such as spray or flash drying Schematic representation of the co-processing method shown in figure.1

**METHODS OF COPROCESSING :**

1.4.1 Spray drying
1.4.2 Solvent evaporation
1.4.3 Crystallization
1.4.4 Melt extrusion
1.4.5 Granulation/Agglomeration

1.4.1 Spray drying:
This spray drying technique allows the conversion of feed from a fluid state into dried particles. The feed can be a solution, suspension, dispersion or emulsion. The dried product can be formed in the powders, granules or agglomerates and these are dependent upon the physical and chemical properties of feed and the dryer design. Final powder properties are required. It is a continuous particle processing drying operation. The spray drying process parameters like inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in feed, disc speed can be helpful in designing a particle with desired characteristics. Hence, spray drying process can be designed as consisting of four steps:[8]

- Atomization of the liquid into droplets.
- Contact of the droplet with the warm drying gas.
- Fast evaporation of the droplets to form dry particles.
- Recovery of the dry particles from the drying gas, using a cyclone.

Advantages of spray drying:
- Possibility to associated non-missible products in continuous operation.
- It allows blending and drying simultaneously solubles and insolubles compound.
- Provides opportunity to fix and protect sensitive active compound on natural carrier.
- Improves hardness and compressibility.
- Enhances machine tableting speed, decreases disintegration time.

1.4.2 Solvent evaporation:
The process is carried out in liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in coating polymer solution with agitation. The core coating material mixture is dispersed in liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated to evaporate the liquid vehicle temperature is reduced to ambient temperature with continued agitation. At this stage microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may be either water soluble or water insoluble materials.[9]

1.4.4 Melting extrusion:
Melt extrusion is a process of formation of small beads, pellets from the molten mass which is extruded through extruder. Extruders consist of four distinct parts: [4]

1. An opening through which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
2. A conveying section (process section), which comprises the barrel and the screws that transport, and where applicable, mix the material.
3. An orifice (die) for shaping the material as it leaves the extruder.
4. Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product. Example: Compressol S [Mannitol, Sorbitol] [8,29]

Advantages
- Excellent repeatability.
- Complicate and intricate shapes are possible.
- Time required is less.

Disadvantages
- Equipment and die cost high.
- Minimum economic length high.[3]

1.4.5 Granulation/agglomeration:
Granulation is the (natural or artificial) process of formation of solid crystals precipitating from a solution, melts or more rarely deposited directly from a gas. For crystallization to occur from a solution it must be supersaturated. This means that the solution has to contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution). This can be achieved by various methods, with (1) solution cooling, (2) addition of a second solvent to reduce the solubility of the solute (technique known as antisolvent or brown-out), (3) chemical reaction and (4) change in pH being the most common methods used in industrial practice. Example: Sugar Tab [Sucrose, Invert sugar]. [8,29]
Advantages

- It eliminates the use of water or any other solvent.
- Short processing time.
- It can be suitable for conventional equipment.

1.5 ADVANTAGES OF COPROCESSING\(^{(8,28)}\)

- Controlled optimal particle size and particle size distribution ensure superior flow properties or coprocessed excipients without the addition of glidants.
- Improving flow properties.
- Improve compressibility, compactibility.
- Better dilution potential, fill weight variation.
- Reduced lubricant sensitivity.
- It can also improve tablet hardness and decrease disintegration time.
- All coprocessed and adjusted excipients are playing a very important role in the development of easy dosage forms.
- Flow of coprocessed excipients was better than the flow of simple physical mixtures.

1.5.1 Improved compressibility

- Coprocessed excipient used mainly in direct compression because in this process there is an increase in flow properties, which results in improved compressibility.
- The pressure hardness relation of coprocessed excipients, when plotted and compared with simple physical mixtures, showed marked improvement in the compressibility profile.

1.5.2 Better dilution potential

- Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material.
- 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.

1.5.3 Reduced lubricant sensitivity

- Most coprocessed 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.

1.6 COPROCESSED EXCIPIENTS

Some examples of marketed co-processed excipient are provided in Table 1.\(^{[24,26,27]}\)
Table 1: Examples of marketed co-processed excipient

<table>
<thead>
<tr>
<th>COPROCESS EXCIPIENT</th>
<th>TRADE NAME</th>
<th>ADDED ADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose, 3.2% Kollidon 30, Kollidon KL</td>
<td>Ludipress</td>
<td>Low degree of Hygroscopicity, good flowability, tablet hardness independent of machine speed.</td>
</tr>
<tr>
<td>Lactose, 25% cellulose</td>
<td>Cellactose</td>
<td>High compressibility, good mouthfeel, better tableting at low cost.</td>
</tr>
<tr>
<td>Microcrystalline cellulose, silicone dioxide</td>
<td>Prosolv</td>
<td>Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability</td>
</tr>
<tr>
<td>Microcrystalline cellulose, guar gum</td>
<td>Avicel CE 15</td>
<td>Less gritiness, reduced tooth packing, minimal chalkiness, creamier mouth feel, improved overall palatability.</td>
</tr>
<tr>
<td>Calcium carbonate, Sorbitol</td>
<td>FormaXX</td>
<td>Controlled particle size distribution</td>
</tr>
<tr>
<td>Microcrystalline cellulose, lactose</td>
<td>microcelac</td>
<td>Capable of formulating high dose, small tablet with poorly flowable active good flow.</td>
</tr>
<tr>
<td>90% Microcrystalline cellulose, 10% mannitol</td>
<td>Avicel HFE 102</td>
<td>Better Flow properties, better tabletability at slower speed</td>
</tr>
<tr>
<td>Microcrystalline carboxy methyl Cellulose</td>
<td>Avicel CL 611</td>
<td>Impart a thixotropic viscosity profile, increase formulation stability across a wide range of PH use as stabilizer</td>
</tr>
<tr>
<td>Starch w/w, gelatinisation aid &amp; Surfactant</td>
<td>Pregelatinised starch</td>
<td>Binder, diluent in oral capsule and tablet. having enhance flow and compression characteristics. tablet binder in dry compression.</td>
</tr>
<tr>
<td>α-lactose monohydrate &amp; β cyclodextrin</td>
<td>Not recognised</td>
<td>Good flowability, compressibility &amp; compactibility. limitations of β cyclodextrin for it flowability &amp; lubrication sensitivity is overcome.</td>
</tr>
<tr>
<td>Lactose, Polyvinylpyrrolidone</td>
<td>Crosspovidone / Ludipress</td>
<td>An excellent filler binder with very high dilution potential &amp; good binding property.</td>
</tr>
<tr>
<td>HPMC, lactose</td>
<td>Not recognised</td>
<td>Improve flowability, &amp; compressibility</td>
</tr>
<tr>
<td>Sucrose, 3% Dextrin</td>
<td>Dipac</td>
<td>Use for direct compressible tablet, improve flowability.</td>
</tr>
<tr>
<td>Sucrose 3% dextrin, Microcrystalline cellulose, Silicon Dioxide</td>
<td>Dipacprosolv</td>
<td>Directly compressible, better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability.</td>
</tr>
<tr>
<td>95% β lactose, 5% lactitol</td>
<td>Pharmatose dec 40</td>
<td>High compressibility</td>
</tr>
<tr>
<td>Orocell 200 with 90% mannitol</td>
<td>Orocell 200 &amp; orocell 400</td>
<td>A development filler binder with high dilution potential and good disintegrating property useful for oral disintegrating tablet</td>
</tr>
<tr>
<td>Microcrystalline cellulose 89%, hydroxypropylmethyl cellulose 2%, &amp; crosspovidone 9%</td>
<td>panExceaatMC200G</td>
<td>Strong intraparticle bonding bridges between the components, improved the blending, rapid disintegration time.</td>
</tr>
<tr>
<td>1-O-Dglucopyranosyl, 6-D glucopyranosyl D-sorbitol (1:3) particle size 90%, 50%.</td>
<td>Isomalt galen IQ-721</td>
<td>Highly soluble agglomerated spherical isomer for fast dissolving and fast disintegration time</td>
</tr>
<tr>
<td>Mannitol 84% crosspovidone 16% silicon dioxide &lt; 1%</td>
<td>pharmabursttMCCL</td>
<td>High compactibility, high loading in small diameter tablets, smooth mouth feel, rapid disintegration time</td>
</tr>
<tr>
<td>Mannitol particle size 60%</td>
<td>Manogem™ EZ</td>
<td>Assist in formulating difficult to use non hygroscopic orodispersible tablet containing find drug</td>
</tr>
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REFERENCES:


