SHORT REVIEW

Pharmaceutical

COPROCESSED EXCIPIENTS-PREPARATION AND FUNCTIONALITIES

KEY WORDS: functionalities, coprocessed excipients, coprocessing, compendial and non-compendial excipients.

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ABSTRACT

With the advancements of tablet manufacturing techniques, the urge to develop and produce high, multifunctional excipients have been increased to meet the set of functionalities. The functionality of the coprocessed excipients enhances the manufacturing process and as well improves quality, performance of tablets. Coprocessed excipients are defined as the mixture of two or more than two excipients that possess specific potential advantages which cannot be produced by simple physical mixing of same combination of excipients. The aim of this review is to focus on advantages, preparation methods of coprocessed excipients. Coprocessing is a technique, where these compendial or non compendial excipients are modified physically in a special way without changing their chemical structure. This review article discusses the need for developing coprocessed excipients, advantages of coprocessed excipients, different methods of preparation of coprocessed excipients and functionalities of coprocessed excipients.

INTRODUCTION:

Manufacturing of tablets has become one of the major profits in the market due to all considered functionalities using different techniques. Direct compression process being primary priority as alternative technique to granulation compression because of its integrity and cost efficiency [1].

- **Necessity Of Coprocessed Excipients:**

There are various categories of excipients which include; single existent excipient, a physical co-mixture of numerous excipients, a novel chemical existent excipient and coprocessed excipients. Enormous investment is needed to develop a novel chemical entity. To conquer this issue, scientists implemented co-processing the excipients that offers various advantages which are not accomplished using simple physical co-mixture of similar excipients [2]. Coprocessed excipients are defined as the mixture of two or more than two excipients that possess specific potential advantages which cannot be produced by simple physical mixing of same combination of excipients.

- **Steps Involved In Obtaining Coprocessed Excipients:** [3]

Identification of (analyzing the particle size required) and selecting desired proportion of excipients to be coprocessed (as per functionality requirements and material characteristics)

Selecting suitable coprocessing technique (melt granulation, roller compaction etc.)

Finally, product with aimed functionalities is obtained using many optimization methods and design of experiments (DOE).

Advantages Of Coprocessing The Excipients With Regard To Functionalities Of Coprocessed Excipients [1]:

- **No Change in chemical structure:**

Several studies based on chemical properties of excipients after coprocessed have been considered. It was found that the x-ray diffraction, IR spectroscopy, NMR, Raman spectroscopy and C13 NMR spectroscopy studies of SMCC [contains micro crystalline cellulose (MCC) and colloidal silicon dioxide] resulted in no chemical changes and shows similar physicochemical properties of MCC. During development phase, this absence of chemical change helps in reducing the regulatory concerns of respective companies.

- **Better Dilution Potential:**

The ability of the excipient to retain its compressibility even when diluted with other low compressibility material is called dilution potential. Generally, excipients should have better compressibility as most of the active drug substances are poorly compressible to retain good compaction even after being diluted with low compressible materials. Cellactose (coprocessed excipient with cellulose and lactose) has found to be having higher dilution potential when compared with the physical mixture of its constituent excipients (i.e. cellulose and lactose).

- **Improved Flow Properties:**

The demand for functionalities of excipients mainly in terms of flowability and compressibility has increased due to the development of high performance tableting machines and direct compression method as attractive preference for tableting. Coprocessed excipients have found to be having better flowability when compared with individual excipient component and simple physical mixture of the same combination of excipients. A detailed study of flow properties of cellactose were performed and the results showed that cellactose is having better flow properties than cellulose and lactose or a simple physical admixture of cellulose and lactose.

- **Reduced Lubricant Sensitivity:**

Generally, most coprocessed excipients are made up of large quantities of brittle material and small quantities of plastic material. Plasticity imparts good bonding properties by creating steady matrix with availability of large surface for bonding. The brittle material yields low lubricant sensitivity as it halts the rational lubricant network formation which creates new exposed surfaces after compression and thus breaks the lubrication network.

- **Fast Disintegration:**

One of the requirements for formulation of orally disintegrating dosage form and immediate release dosage forms is fast disintegration. Due to high swelling, solubility and imbibing properties of coprocessed excipients, they deliver rapid disintegration to the developed formulation.

- **Fill Weight Variation:**

Generally, fill weight variations tend to occur for materials during direct compression due to poor flow properties. Coprocessed excipients have less fill- weight variations when compared with simple mixtures of its constituent excipients or compendial materials. The reason behind the better flow properties of coprocessed excipients is permeation of one particle into matrix of another particle, reducing the rough surfaces of particles and creating a near-foremost size distribution. Fill weight variation were performed for SMCC and MCC with various machine speeds and results showed that SMCC has less fill-weight variation than MCC.

- **Improved Compressibility:**

Coprocessed excipients tend to have better compressibility profile compared to simple physical admixture of its constituent excipients when a graph plotted with respect to pressure- hardness relationship. Studies showed that the compressibility studies of cellactose, ludipress and SMCC are better than the simple physical mixtures of same combination of excipients.

Different Methods For Preparation Of Coprocessed Excipients:

The various techniques applied for obtaining coprocessed excipients are briefly presented as follows:

- Spray drying
- Melt granulation
- Wet granulation
- Co-precipitation
- Solvent evaporation
- Milling
- Dry granulation/Roller compaction

Spray Drying:

Coprocessing of excipients through spray drying method includes production of fine droplets by atomizing the feed, which might be the suspension or solution. These fine droplets are rapidly dried by spraying them into the steam of hot gas. The formation of spherical particles is due to the increase in droplet surface area and high temperature, which makes them suitable for the direct compression method. Excipients such as MCC, Colloidal silicon dioxide are coprocessed using spray drying technique which is used as dissolution stability enhancer [4].

Melt Granulation:

Melt granulation method of coprocessing includes the mixing of blend of excipients with a binder (which is solid at a room temperature but melts at 50-80°c). This above mixture is heated with continuous blending so as to breakdown the mass into aggregates. These aggregates are cooled down to room temperature followed by screening to achieve granules of preferred size. Calcium phosphate with fatty acid wax (glyceryl palmitostearate) is coprocessed using melt granulation technique which has the advantage of overcoming abrasiveness and issues associated during capping for calcium phosphate [5].

Wet Granulation:

Wet granulation method is a simple, convenient and cost effective method of coprocessing the adjuvant production. This technique, involves wetting of the mass blend of excipients to be coprocessed with a binder solution, screening of wet mixture, drying of soggy granules followed by sifting of dry granules. The most common equipments used for wet granulation are fluid bed granulator and high shear mixers. Cellulose with crospovidone and cellulose with insoluble CMC are coprocessed using this technology which have an application of improving bulk density [6].

Co-precipitation:

Any technique used like wet/dry granulation, pH change, freeze drying or simple solution mixing can be used to coprocess the excipients by co-precipitation method. Co-precipitation technique by pH change method was developed for coprocessing corn starch with colloidal silica. An alkaline solution of colloidal silicon dioxide is prepared, to this solution corn starch was added slowly with extreme stirring. The pH of the above mixture was adjusted to pH~7 using hydrochloric acid. The solid particulates obtained were then filtered out and dried up in the oven [7].

Solvent Evaporation:

This procedure involves the dispersion of powder blend to a suitable solvent through agitation to achieve desired microcapsule size. All the solvent gets evaporated by application of heat. The dispersion was dried and dry granules are passed through desired sieve. Excipients like chitosan and Eudragit S-100 are coprocessed using this method which has an application of developing venlafaxine HCL sustained release tablets [8].

MILLING:

Coprocessing of excipients by milling technique can be performed by roller mill, ball mill, jet mill, hammer mill, bead mill or mile stone mill. Milling technique involves premixing of excipients followed by passing this mixture through the rapid milling machine. As this mixture is subjected to pass through mill, due to force, the particles come in contact with each other and develop bonds. Coprocessing of Cross-linked polyvinyl pyrrolidone and calcium silicate was one of the examples developed through milling technique [9].

DRY GRANULATION/ROLLER COMPACTION:

During this process, the powder blend of excipients is compressed between two rotating rollers. The resulting compacted mass is milled into granules. This procedure is the best technique for handling moisture sensitive or heat sensitive excipients as no addition of liquid step is involved. Dry granulation method has been adopted for coprocessing polyox WSR-301 and HPMC K4M, was applied to develop metformin HCL sustained release tablets [10].

Excipients coprocessed in the literature are presented in table 1 as follows:

Table 1: Some Examples Of Coprocessed Excipients [8]

Coprocessed Excipients	Method	Benefits
Lactose PVP Crospovidone	Spray drying	Great hardness, good compressibility and flow properties
Lentinus tuber regium Sodium bicarbonate Tartaric acid	Solvent Evaporation	Good dilution potential
Di calcium phosphate Carboxymethyl cellulose	Co-precipitation	Improves flow properties
Calcium carbonate Sorbitol	Direct compression	Controlled particle size distribution
Crospovidone Sodium starch glycolate	Wet granulation	Exhibits good compaction and disintegration properties
Microcrystalline cellulose Guar gum	Direct compression	Less chalkiness, Minimal grittiness

CONCLUSION:

In this article we conclude that Co-processing results in developing stable formulation with improved physical, chemical and mechanical properties. Co-processing is interesting because the products are physically modified in a

special way without altering the chemical structure. In this article brief information on different types of coprocessing the excipients, offers majority of advantages which benefits pharmaceutical formulations. Various coprocessed excipients along with the benefits, available in the literature were discussed. As developing coprocessed excipients has major contribution to reduce use of multiple excipients in the formulation, upcoming drug delivery in future looks promising. Co-processed excipients are believed to bring a drastic change in the field of pharmaceutical Research.

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