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MULTIFUNCTIONAL EXCIPIENTS: A NEW TREND OF EXCIPIENT TECHNOLOGY

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Abstract:
The pharmaceutical industry demands innovation in a short period of time so as to gain the access to new products in market. The major requirement for direct compression process is selection of excipients with optimum physical characteristics which improve the tablet blend's final flow and compressibility. Co-processed excipient has gain popularity in formulation development of various dosage forms. The goal of this review is to discuss the emergence of co-processed excipients in pharmaceutical manufacturing as a new trend in excipient technology. Co-processing is a novel concept of combining two or more excipients that posses specific advantages. The review discusses about the sources of new excipients, potential advantages, material characteristics, various methods of preparation, description of some available co-processed excipients.

Key words: *Co-processed excipients, Direct compression, Pharmaceutical manufacturing, Co-processing.*

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INTRODUCTION:

Tablets are the most commonly used dosage forms in pharmaceutical industry because they can be accurately dosed and provide good patient compliance, they are easy to manufacture, and they can be produced at a relatively low cost and owing to its stability**,** dose uniformity, user acceptability. Excipients play an important role in drug formulation processes and perform a wide range of functions to offer desired properties for the finished drug formulation and more effective and safer finished products for patients. Combination excipients fall into two broad categories: Actual mixtures and the excipients co-processed.

As the name suggests, physical mixture are simple admixtures of two or more excipients usually formed by low-shear processing of short duration. These can be either liquids or solids and are usually used for convenience rather than to promote the manufacturing process or improving the resultant pharmaceutical product. Examples of such physical mixtures include dispersion powders for immediate release of film coating which reduce the time needed to prepare film coating suspensions and minimize the final product color variation. Such physical mixtures are not suitable for consideration for National Formulary (NF) monographs because the individual components are separated (distinct and intact) before mixing; i.e., the manufacturing process of each component has been completed and these components can therefore be properly monitored before mixing.

A co-processed excipient is a mixture of two or more excipients engineered to alter their physical properties in a manner that cannot be accomplished by simple physical mixing, and without substantial chemical change. By formulating few excipients into a single composite material using a specific manufacturing process, the quality of the end product is enhanced. This has become a newer trend in the development of formulation. They have been used to improve various properties of dosage forms so, it can be used in almost any dosage type, but mostly in solid dosage form. They are also referred to as excipients of multifunctional or high efficiency.

ADVANTAGES OF CO-PROCESSING

i. Improved compressibility

It is an essential factor in the development of tablets. Ideally, once the compression force is removed, a compacted tablet will be created. Nevertheless, this plastic property is absent from all traditional tablet excipients. This weakness is resolved by the majority of co-processed excipients.

ii. Better dilution potential

Dilution potential is defined as the excipient's ability to maintain compressibility, even when diluted with another low compressibility material. The compressibility of the API and many inactive excipients is low. Other side, a co-processed excipient with high dilution potential is ideal so that even when mixed with other excipients, the compressibility properties of the powder blend mixture can be preserved.

iii. Reduced lubricant sensitivity

Generally, hydrophobic lubricant typically has negative impact on powder mix compression behaviour. Plasticity refers to an excipient's delicate attribute. The existence of a large degree of brittle character during a co-processed excipients offers the lubricant a low sensitivity as a result of it prevents the formation of a coherent lubricant network by the compression of forming newly exposed surfaces, breaking the lubricant network.

iv. Ease of production

Co-processed excipient simplifies the tablet formulation and production phases. Tablet preparation usually consists of weighing of active ingredient and various excipients accompanied by mixing, granulation, drying, sieving, and compression. Weighing of each ingredient might be time-consuming, and it may incur error in the process can occur. Using a co-processed excipient can simplify the production process and reduce the error rate.

v. Improved flow properties

Compared to its individual constituent or physical mixture, the co-processed excipient is stated to have better flow properties by regulating the particle size distribution. Good flowability is desired especially for high-speed rotary tablet machines. The excipients co-processing plays an important role in enhancing the flow property of the compressed powder mass.

vi. Fast disintegration

Quick disintegration is compendial and formulation prerequisite for immediate release and orally disintegrating dosage form. Co-processed adjuvants, provide rapid disintegration into the formulation produced due to their high solubility, swelling and wicking properties.

vii. Stability

The excipient co-processed should be physically and chemically stable. The used ingredients should be inert and should not interfere with the API.

viii. Cost saving

The manufacturer uses a single excipient with many functional properties, reducing the number of excipients used and labor costs involved in processing them other than the direct compression form. The use of co-processed adjuvants simplifies

the production process, resulting in improvements in time and costs.

NEED OF MULTI-FUNCTIONAL EXCIPIENTS

1. **Effective use of existing excipients:** Identifying new applications for existing excipients may be a comparatively low cost and less time-consuming method compared to a totally new development.
2. **Excipients with desirable properties:** There are a variety of existing excipients missing in some formulations and a few of the desirable properties needed.
3. **Drugs developed through genetic engineering**: If new drugs are being formulated with existing excipients there is often a major question about their compatability. Therefore, it will take new excipients to solve these problems.
4. **Advances in production process and equipment:** Changes within the pharmaceutical manufacturing processes and equipment systems, particularly increases in low-cost production rates, lead to the need for new excipients.
5. **Patient or subject compliance:** For patient safety and comfort reasons, some excipients which are used now-a-days are unacceptable. Lactose deficiency arises in individuals, who are deficient within the enzyme lactase, resulting in abdominal cramps, diarrhea, distension and flatulence.
6. **Specialized drug delivery systems:** Special excipients are required to develop new or specialized drug delivery systems. For instance, metered dose inhalation devices require specific size grade excipients and oral strip preparation growth.

GENERAL STEPS IN DEVELOPING CO-PROCESSED EXCIPIENTS

To design a new co-processed excipient that meets a particular applications functionality requirement, it is important to consider a few steps.

a. Identification of the excipients group to be co-processed

A good co-processed excipient should examine the balance between material's plasticity and fragility. Plastic and brittle material combination nullifies the storage during compression of undesirable elastic energy. This will produce a product with a small amount of relaxation of stress and a reduced tendency of capping and lamination and thus optimum performance of tableting. The combination of the selected excipient would complement each other and have synergistic effect for achieving the desirable characteristics.

b. Assessing the particle size

Particle size can affect the compressibility and flowability of the end product. If the participating excipients differ in the initial particle sizes, the emphasis should be on generating the final co-processed adjuvant of uniform particle size.

c. Choosing an effective technique to co-process various excipients

Other co-processing processes such as wet granulation, melt granulation, freeze drying, spray drying, hot melting extrusion. In this analysis, a detailed description was given later.

d. Optimisation of the process and the percentage of each excipient

This may contribute to functionality variations in the end product functionality. In order to achieve a final product with desired functionalities, different optimization techniques and experimental designs with sound statistical analysis can be used.

SOURCES OF NEW EXCIPIENTS

- The development of new chemical excipients, new grades and new combinations of existing materials can be used to produce excipients with enhanced functionality.
- Any new chemical excipient should be subjected to different levels of regulatory approval to resolve health and toxicity concerns, which is a long and expensive process. The excipient also has to undergo a generic development, which shortens the duration of market exclusivity.
- Because of the marginal returns from the latest excipients, the high risk and significant investment involved are not justified.
- For excipients, a feasible alternative must be created together by pharmaceutical manufacturers, during which a new excipient is part and parcel of the possible new drug application. This form has already been successfully applied in delivery area, where CyDex and Pfizer have worked together to secure a solubilizer approval.
- The combined experience of pharmaceutical and excipient companies will lead to the development of novel excipients tailored to the needs of individuals.

- The development of new grades of existing excipients (physicochemical) has been the most effective technique for the development of new excipients over the past three decades, an approach allowed by the introduction of better grades of excipients like pre gelatinized starch, crosscarmellose, and crosspovidone.
- Nonetheless, due to the limited range of possible changes, performance can also be changed to some degree. Because all formulations include several excipients, a new combination of existing excipients is an interesting option to boost excipient functionality. To get the optimal set of performance characteristics. Several different combinations of known excipients can be used.
- Nonetheless, the development of these combinations is a complex process as one excipient may interfere with another excipient's existing functionality.
- Over the years, the development of co-processed excipient combinations at the subparticle level has become increasingly important.
- In the following section of this article, which discusses particle engineering, new physical category of existing excipients and co processed excipients are further explored.

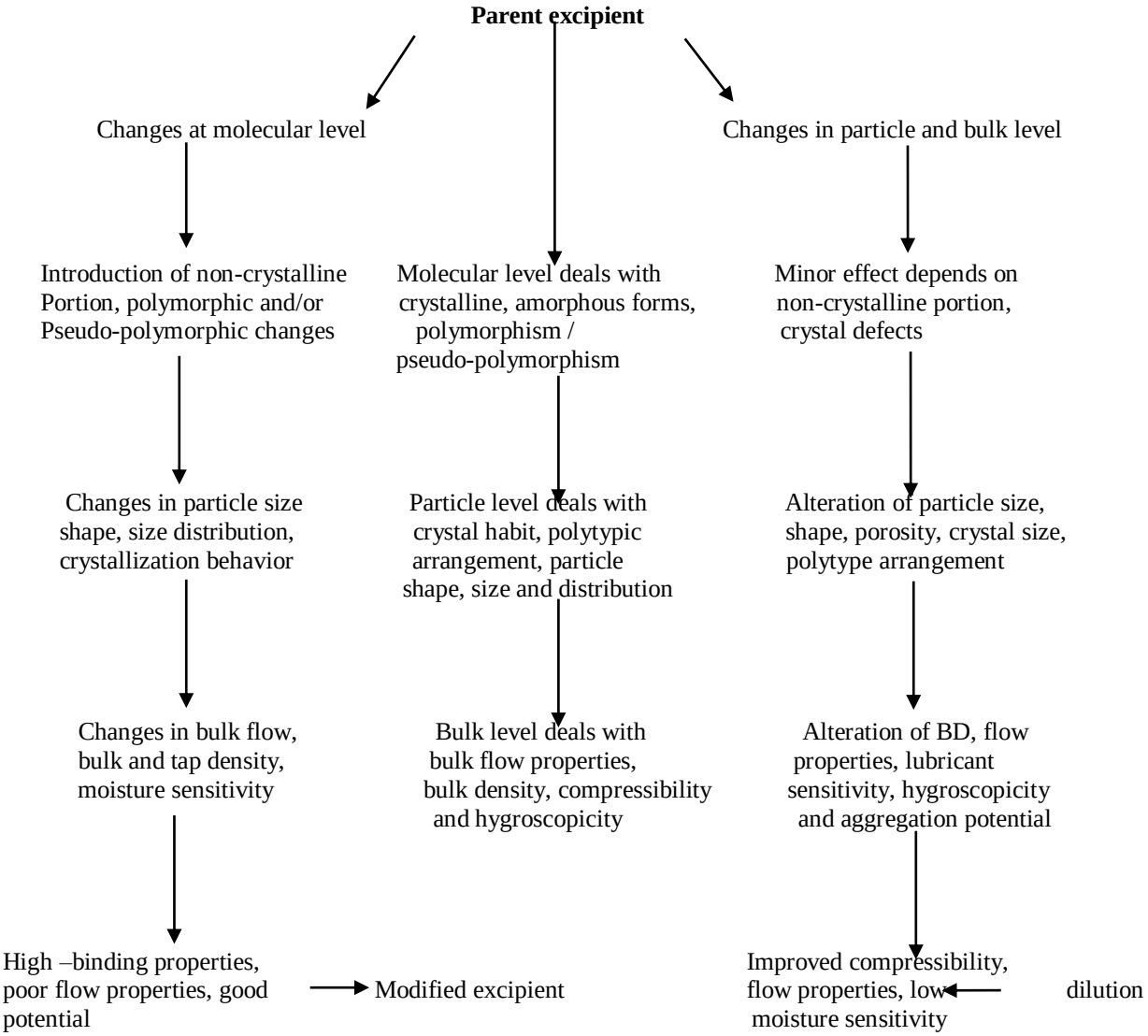

Figure 1: The pyramid of solid state

Particle engineering as source of new excipients

- Three solid state levels describe solid substances: the amount of molecules, particles, and mass. Both the levels are closely linked to each other, representing the shifts at one level at another.
- The molecular level involves the structure in the crystal lattice of individual molecules and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state.
- Particle level includes individual properties of particles such as shape, size, surface area, and porosity. The majority level consists of an ensemble of particles and properties.
- Fundamental solid-state properties of the particles like composition, particle size, shape, surface area, porosity, and density influence the excipient functionality like flowability, compactability, potential for dilution, potential for disintegration, and lubricating potential.
- Therefore, the creation of a new excipient must begin with a particle design appropriate for the functionalities required.
- Different arrangements of crystal lattice will generate particles with different parameters by playing parameters such as crystallization and drying conditions may produce particles with different parameters. Lactose is an example of that approach being applied successfully.
- However, particle engineering of a single excipient can only provide a limited amount of enhancement in functionality.
- Co processing is based on the novel concept of two or more excipients interacting at the sub particle level, with the goal of synergizing improvements in functionality and to mask the undesirable properties of individual excipient.
- The availability of a large number of co processing excipients means multiple possibilities for tailor-made "designer excipients" to meet specific functionality criteria or enhance the desired excipient properties.
- For instance, if a material is used as a filler and binder has a low property of disintegration, it can be co- processed with another excipient with good wetting properties and high porosity because these attributes will increase the absorption of water, which will allow the tablets to disintegrate.

Table 1: Different particle properties affecting excipient functionality

Particle property	Excipient functionality
Enlargement of particle size	Flowability, compressibility
Restricting particle size distribution	Segregation potency
Enlargement of particle porosity	Compressibility, solubility
Surface roughness	Flowability, Segregation Potency

Co-processing of excipients

The actual development process for a co processed excipient includes the following steps

1. Identifying the excipients group to be co processed by evaluating the material characteristics and criteria for functionality.
2. Choosing the proportions of different excipients.
3. Assessing the particle size needed for a co-process. This is particularly important if one of the components is handled during a dispersed phase. After processing the latter's particle size depends on the size of it's original size.
4. Choosing a suitable drying method like spray or flash drying to maximize the method (because even this could result in functionality variations).

Considering material characteristics in coprocessing

Material science plays a significant role in altering a material's physico-mechanical characteristics, particularly in terms of its compression and flow behavior. Coprocessing excipients can be categorized as elastic, plastic, or brittle materials by providing an interesting method to modify these physico-mechanical properties by virtue of their reaction to applied forces. In the truest sense, it is difficult to group products entirely into one category. Pharmaceutical materials display all three types of behavior, the main reaction being one type. This makes it hard to distinguish which property is good for compressibility. Coprocessing is generally done with one rigid excipient and another brittle excipient. Maarschalk reports that coprocessing is conducted with a large quantity of brittle material and a small quantity of plastic material, as Cellactose indicates (Meggle Corp.) whereever 75% of the lactose (brittle material) is coprocessed with 25% of the cellulose (plastic material). That specific combination prevents

an excessive amount of elastic energy from being maintained throughout compression, resulting in a small amount of stress relaxation and a decreased capping and laminating tendency. Examples of the other extreme, however, still occur (for example, SMCC has a large amount of MCC [plastic material] and a small amount of silicon dioxide [brittle material]). Such two examples illustrate the fact that coprocessing is usually done using a combination of materials plastic deformation and brittle fragmentation characteristics. For optimum tableting performance a combination of plastic and brittle materials is required. Therefore, by selectively overcoming the drawbacks, coprocessing these two types of materials provides a synergistic effect, which in terms of compressibility, may help improve functionalities such as compaction efficiency, flow properties, sensitivity to strain-rate, lubricant sensitivity or moisture sensitivity, or reduced hornification.

Properties and advantages of the co processing excipients

Many authors documented the benefits and potential disadvantages of the co processed excipients properties, such as SMCC, Cellactose, and Ludipress

a) Absence of chemical change

Many detailed studies of chemical properties of excipients after co processing have shown no chemical change to those excipients. Detailed SMCC studies with X-ray diffraction analysis, solid state nuclear magnetic resonance (NMR), IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy haven't detected any chemical changes and show a similarity to MCC's physicochemical properties. This lack of chemical change helps to reduce regulatory issues for a product during the development phase.

b) Physico-mechanical properties

1. Improved Flow Properties

Controlled optimum particle size and particle-size distribution ensure superior flow properties without the utilization of glidants for the co-processed excipients. The volumetric flow properties of SMCC are studied as compared with MCC. Such excipients particle size were found to be approximately identical to those of the parent excipients, but the flow of co processed excipients was greater than the flow of simple physical mixtures. A comparison of the Cellactose flow properties was also performed. The angle of repose and therefore the Hausner ratio were measured, and it had been found that Cellactose had better flow characteristics than lactose. The spray-dried product had a spherical shape and even surfaces, thus improving the flow properties as well.

2. Improved compressibility

Coprocessed excipients were primarily utilized in direct compression tabletting because the flow properties and compressibility profiles are netly increased during this process and therefore the excipient produced may be a filler–binder. When plotted and contrasted with simple physical mixtures, the pressure-hardness relationship of the co-processed excipients showed a marked improvement within the compressibility profile. Compressibility efficiency of excipients like Cellactose14, SMCC15-16 and Ludipress17issuperior to the simple physical mixtures of their constituent excipients. Although direct compression appears to be the most preferred method for pharmaceutical development, wet granulation remains favored, as it has the potential benefits of accelerating flow properties and compressibility when an additional granular binder is added, and it achieves better content uniformity for low-dose drugs. Excipients like MCC lose compressibility when adding water, which may be a phenomenon called quasihornification. Nevertheless, this property is improved when co-processed into SMCC.

3. Better dilution potential

Dilution potential is the excipient's ability to maintain a compressibility even though when diluted with another material. Most active drug substances are poorly compressible, which ends up in better compressibility properties for excipients even when diluted with a poorly compressible product to maintain good compaction. Cellactose is shown to have a greater dilution potential than the constituent excipients physical mixture.

4. Fill weight variation

Direct compression materials generally tend to point out high fill weight variations due to poor flow properties, but it is shown that co-processed excipients have less fill-weight variation problems compared to simple mixtures or parent products. The primary reason for this effect is that one particle is impregnated into another matrix, which decreases the surfaces of the rough particles and produces a near-optimal size distribution, resulting in better flow properties. With high-speed compression machines the fill-weight variation tends to be more prominent.

5. Reduced lubricant sensitivity

Several co-processed products contains a comparatively great deal of the brittle material like lactose monohydrate and a smaller amount of the plastic material like cellulose fixed between or on brittle material particles. The plastic material offers good bonding properties as it creates a continuous matrix with a large bonding surface. The large quantity of brittle material offers low sensitivity to lubricants because it prevents the creation of a cohesive lubricant network by shaping newly

exposed surfaces after compression, thereby breaking up the lubricant network.

6. Other properties

Co-processed excipients offer the following additional advantages:

- Pharmaceutical manufacturers choose to use a single excipient with many functional properties, minimizing the inventory number of excipients.
- Improved organoleptic properties such as those found in the co processed MCC excipient Avicel CE-15 (FMC Corp., Philadelphia, PA),and guar gum have been shown to have distinctive advantages in chewable tablets in terms of reduced grittiness, reduced tooth packing, minimal chalkiness, enhanced mouth feeling, and enhanced over all palatability.

Various methods of preparation of multi-functional excipients

Roller compaction uses the dry granulation method for bonding to particles. This approach is useful for moisture and heat sensitive materials. The powder blend is uniformly mixed and compressed between counter-rotating rollers to form a ribbon of compacted material which is then milled into particle size granules.

Wet granulation

Wet granulation is a conventional and simple method for the co-processed processing of adjuvants. Fluid bed granulators and high-shear mixers are two devices which are widely used for the same. Throughout fluid bed granulation, a flow of air pumped upwards through the granulator's bottom panel exposes the powder mix to fluidization. The binding solution is sprayed onto the powder bed in the opposite direction to the air flow. The solid particles are combined with the liquid droplets and hit the bed resulting in adhesion and ultimately granule formation. Partial drying by the fluidizing air occurs continuously throughout the granulation.

For high-shear granulation, the powder is held in a closed vessel by an impeller in agitation. This binder solution is sprayed from the top. High shear force prevents the production of large agglomerates. Dry up occurs in the same system with the new single-pot technology. The granules that formed are significantly denser than those obtained in the granulation of the fluid bed.

Hot melt extrusion

Hot melt extrusion uses heat which exceeds 80 °C. This approach does not work for thermo- labile materials. The excipients are melted and then pressurized and solidified into a variety of shapes through the die. The solvent is not required in the process as the molten polymer will act as a thermal binder.

Spray drying

Spray drying typically involves five steps: Feedstock concentration, atomization, droplet-air contact, droplet drying and separation and collection of droplets. This technique converts a feed that could be a solution, suspension or dispersion into dried particulate form by spraying it into a hot drying medium. The excipient bonding of particle-particles occurs during the process. The increased droplet surface area and high temperature lead to the formation of spherical shape particles with enhanced flowability and an acceptable application of direct compression such as Starlac®.

Roller drying

The homogeneous solution or dispersion comprising the pre-blended excipients is dried with a roller dryer. This method was used by Meggelaars *et al.* (1996) to co-process lactose with sorbitol and lactitol. The temperature used was high to get an end product consisting primarily of β-lactose in crystalline form.

Co-transformation

Co-transformation technique involves applying the heat or solvent effect to "opened up" (swelling) particles in one excipient. The other excipients are inserted into the aforesmentioned excipients "open-up" framework. The modified excipient enhances end product functionality.

Milling

Milling or dry grinding can be achieved with a roller mill, ball bill, bead mill, millstone mill, jet mill or a hammer mill. The excipients are premixed with a high-speed milling machine. The particles come into contact with each other during the milling process and form bonds when forced to mill or pass through the screen. Rao *et al.* (2012) used this technique for the co-processing of cross-linking polyvinylpyrrolidone and calcium silicate.

Melt granulation

The excipient blend is mixed with a meltable binder (normally under 80˚C at a solid state). To break the mass into agglomerates, the mixture is subjected to heat above the binder melting point with continuous blending. Eventually, the cooled agglomerates are screened to get granules of desired size.

Solvent evaporation

Solvent evaporation takes place in an exceedingly liquid manufacturing vehicle. The coating excipient is dissolved in an volatile solvent that is incompatible

with the liquid manufacturing vehicle, followed by dissolving or dispersing the core excipient within the coating solution. Agitation force is applied to attain the required encapsulation size. Heat is employed to evaporate the solvent.

Table 2: Products of co-processed excipients which are available in the market

Trade name	Excipients	Manufacturer	Uses
Ludipress	Lactose, kollidon 30, kollidon CL	BASF	Low degree of hydroscopicity, good flowability, hardness of the tablet, independent of the machine speed
Cellactose	Lactose and cellulose	Meggle	High compressibility,good mouth feel, better tableting at low cost
Starlac	Lactose and maize starch	Meggle	Good flowability due to spray drying the acceptable crushing force due to lactose content and rapid disintegration on starch
Prosolv	MCC and silicon dioxide	Penwest pharmaceuticals	Better flow,reduced sensitivity to wet granulation,better hardness of the tablet,reduced friability
Pearlitol SD	Granulated mannitol	Roquette	Suitable for chewable tablet application with good mouthfeel and palatability
Ludiflash	Mannitol, crospovidone and polyvinyl acetate	BASF	Suitable for high-speed tableting, low friability, and good flowability
MCC sanaq burst	Pure Microcrystalline cellulose	PharmatransSanaq AG	Filler, binder, disintegrant
Disintequik ODT	Lactose, sucrose, calcium carbonate, microcrystalline cellulose	Kerry	Disintegrant, filler, sweetener
F-melt	D-Mannitol, xylitol , mcc, crospovidon, fujicalin	Seppic	Binder, filler, disintegrant
SmartEx QD100	Mannitol , L-HPC, PVA	ETSU SmartEX	Binder, filler, disintegrant

CONCLUSION:

The co-processed excipients play an important role in formulating stable, result oriented drug delivery system with enhanced physical, chemical and mechanical properties. In addition, co-processed excipients solve the problems of the precompression parameters, compressibility, palatability, disintegration, dissolution, and sticking which conventional individual excipients may have. The co-processed excipient may be a promising tool in pharmaceutical excipient development. The current co-processed adjuvants are unable to fulfill all the functionalities necessary to prepare various novel formulations. Cost is another factor that increased the price of the final product. Therefore, there is enough scope of development of new co-processed excipients to meet pharmaceutical industry demand. Advanced work in academia and pharmaceutical industry is expected to definitely bridge that gap in the near future.

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