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Added Functionality Excipients: Future of Pharmaceutical Industry

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ABSTRACT

Formulation scientists recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately and they have focused their attention on the production of multifunctional excipients with enhanced performance to meet the needs of formulation experts in terms of costs of production, enhanced excipient functionality and quality of tablets. Manipulation in the functionality of the excipient is provided by the co-processing of two or more existing excipients. Tablet manufacturing has been changed by the introduction of the direct-compression process and high-speed machines. These two developments have increased the demands on the functionality of excipients in terms of flow and compression properties. This review article aims to provide a complete overview of recent development in co-processed excipient technology and the approaches involved in the development of such excipients.

INTRODUCTION:

From manufacturers to patients, every party along the pharma supply chain wants to see the market filled with innovative products that advance treatments. The industry as a whole accepts innovation when it applies to final drug products or the active pharmaceutical ingredients (APIs) that give them their potency, but not necessarily the often-overlooked elements that account for the bulk of composition: Excipients.[1]

The term comes from the Latin word excipients, present participle of the verb excipere which means to receive, to gather, to take out.[2]The most important part of medicine as far as its weight is concerned, is constituted by its excipients, which have the important functions of guaranteeing the dosage, stability, and bioavailability of the active principle.[2]International Pharmaceutical Excipients Council (IPEC) defined excipients as the other substances in the pharmaceutical formulation than the active pharmaceutical ingredients (API) which have been appropriately evaluated for the safety to help in processing, manufacturing, protection and give support or to enhance stability, bioavailability or patient acceptability or to assist in product identification or improve any features of the safety or effectiveness of the drug delivery system during storage or use.[3,4] A medicinal product consists of more than just the active drug(s). There are other materials present that are necessary to allow the formulation to be processed or to achieve the desired pharmacological and/or pharmacokinetic effect. These other materials are generally referred to as excipients.

Excipients are therefore fundamental to the design of drug delivery systems whether the drug is intended for bolus administration or controlled release. It is the excipients that allow the formulation scientists to achieve their objective. Without excipients, it is arguable whether the therapeutic revolution could have taken place. Yet excipients have received scant attention from the pharmaceutical industry. Excipients can thus be regarded as the "Cinderella's" of formulation science.[5]

The majority of the excipients that are currently available fail to meet the desired set of functionalities, therefore, creating urgency for the development of high functionality excipients.[6]

In earlier days, excipients were considered inactive ingredients. Over time, pharmaceutical scientists learned that excipients are not inactive and frequently have a substantial impact on the manufacture and quality, safety, and efficacy of the drug substance(s) in a dosage form.

Tablets and capsules are preferred drug delivery vehicles because they can be precisely dosed, easily manufactured, and packaged on a large scale, and can contribute to good patient compliance.[7]

Added functionality excipients facilitate the development of novel drug delivery methods and improve processing techniques. The development of various added functionality excipients (AFEs), which are used to achieve formulations with desired end effects, is equally important.

Obtaining regulatory approval for the use of new excipients and breaking the tradition of conventional formulation development have been two major hurdles in convincing formulators to incorporate new excipients into their formulations.[8]

Despite these challenges, many new AFEs have been successfully introduced and are used in the pharmaceutical industry to date. Compared with existing excipients, the improved physical, mechanical, and/or chemical properties of such AFEs have helped solve formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation.[7]

Excipients (additives) are compounds other than the active ingredients that are intentionally incorporated into pharmaceutical dosage forms. They play specific functional roles in the formulation of dosage forms. As follows:

Functional Uses of Excipients:[9]

- Excipients play a wide variety of functional roles in pharmaceutical dosage forms that include: Modulating solubility and bioavailability of active pharmaceutical ingredients.
- Increasing the stability of active ingredients in the dosage forms.
- Helping active ingredients to maintain preferred polymorphic forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and disintegrants.
- Preventing aggregation or dissociation.

- Modulating immunogenic responses of active ingredients

The corelative relationship between the pharmaceutical and the excipient industries shows that both of them have the same fluctuations in the drug usage trend. In the case of most dosage forms, the quantity of one or more excipients is greater than the quantity of the active pharmaceutical ingredients (APIs) present in them.

Conventional excipients have been replaced with sophisticated compounds that fulfill multifunctional roles in modern pharmaceutical dosage forms such as improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability, and performance of technological functions that ensure ease of manufacture.[2,10,11]

Need of excipients:

The development of new excipients till the date has been according to the market requirement. Excipients are developed first and market requisition is created through marketing approaches and from many years, not a single novel chemical excipient has been introduced into the market.[9,10]The primary cause for this deficiency of new chemical excipients is the relatively expensive cost involved in the excipient's findings and development.[11,12] However, with the increasing number of new drug entities with varying characteristics, there is a growing burden on formulators to develop new excipients to achieve the anticipated set of functionalities.

Most of the excipients that are natural or artificial products do not possess the properties that will impact the API anticipated delivery system upon formulation. No single excipient has all the desired physicomechanical properties for the development of a vigorous drug delivery system. Hence, there is a necessity to have excipients with multi functionalities such as better flow, low/no moisture sensitivity, superior compressibility, and rapid disintegration ability.[12,13]

Particle engineering as a source of new excipients:

Solid substances are characterized by three levels of solid-state: the molecular, particle, and bulk levels. These levels are closely connected, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. Particle level comprises single-particle properties such as shape, size,

surface area, and porosity. The bulk level is composed of collaborative particles and properties such as flowability, compressibility, and dilution potential, which are critical factors in the performance of excipients.

The fundamental solid-state properties of the particles such as morphology, particle size, shape, surface area, porosity, and density influence excipient functionalities such as flowability, compatibility, dilution potential, disintegration potential, and lubricating potential. Hence, the creation of a novel excipient must commence with a particle design that is suited to deliver the anticipated functionalities.

A much broader platform for the management of excipient functionality is provided by coprocessing or particle engineering two or more existing excipients. Coprocessing is based on the novel concept of 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 annoying properties of individual excipients.[14]

Co-processed Excipients:

A co-processed excipient is a combination of two or more compendial or non-compendial excipients designed to physically modify their properties manner not attainable by simple physical mixing, and without substantial chemical change. co-processed excipients are used mainly in solid dosage forms such as tablets, capsules, powder and in liquid dosage forms such as emulsions, suspensions, injections, and in semisolid dosage forms such as creams, ointments, and pastes .[15]

The combining of known excipients at the sub-particle level (also known as co-processing) leads to excipients with revised properties like enhanced surface area, increased porosity, enhanced compressibility, good flowability, etc. co-processed excipients are also suitable for direct compression and thus help in the simplification of tablet manufacturing. The reason for enhanced compressibility can be drawn from the fact that most of the co-processed excipients primarily consist of a large amount of brittle material and a smaller amount of plastic material. Thus, a co-processed material displays the property, which is a combination of plasticity as well as brittleness.[16]

Co-processing of excipients provides products with enhanced properties in comparison to their parent excipients, alone or as a physical mixture. A key objective of Co-processing is primarily at addressing the issues of flowability, compressibility, and disintegration potential,

and most importantly, the development of filler-binder combinations.[7]Co-processing is an additional technique that new excipients are approaching the market without enduring the rigorous safety testing of a completely new chemical.[17] It can be defined as merging two or more recognized excipients by an appropriate process.[18]

Advantages of co-processing:

No Chemical Change:

Co-processing of Excipients will not fetch chemical changes in excipients.

Goyanes A. et al. prepared co-processed MCC-Eudragit E excipient and compared IR spectra of co-processed excipient with its excipient, MCC and Eudragit E. The peaks of individual excipients were retained in spectra of co-processed MCC-Eudragit E which indicated the absence of chemical reaction. X-ray powder diffractograms revealed that the co-processing did not alter the crystallinity characteristics of MCC.[19]

Improved compressibility:

Compressibility is a significant factor of thought in tablet development. Ideally, a compacted tablet is formed once the compression force is removed. However, all the conventional tablet excipients lack this plastic property. The majority of the co-processed adjuvants overwhelmed this restriction.[20]

Flores et al. (2000) reported that the compressibility of Ludipress®, a co-processed adjuvant, is superior to the physical mixtures of their constituent excipients.

The compressibility performance of excipients such Flores L.E. et al Showed Cellactose, Sherwood et.al. showed that SMCC and Schmidt P.C. et.al. showed that Ludipress are superior to the simple physical mixtures of their constituent excipients. Although direct compression seems to be the method of choice for pharmaceutical manufacturing, wet granulation is still preferred because it has the advantages of increasing flow properties and compressibility when an extra granular binder is introduced, and it achieves a better content uniformity in the case of low-dose drugs. Excipients such as MCC lose compressibility upon the addition of water, a phenomenon called quasihornification. This property is improved, however, when it is co-processed in SMCC.[21,22,23,24]

Better dilution potential

Dilution potential is defined as the capability of the excipient to retain its compressibility even when diluted with another low compressibility material. API and many inactive excipients have deprived compressibility. On the other hand, a co-processed excipient with high dilution potential is desirous so that the compressibility properties of the mixture of powder blend can be maintained even when diluted with other excipients .[25]Cellactose® is shown to have a higher dilution potential than the physical mixture of its constituent excipients.[24]For example co-processed lactose and sorbitol.[26]

Lubricant sensitivity

Generally, aquaphobic lubricant provides a negative impression on the compression behavior of powder blends. Plasticity contributes brittle characteristics to an excipient. The presence of a bulky degree of brittle character in a co-processed excipient provides low lubricant sensitivity because it avoids the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus flouting up the lubricant network.

For example, co-processed MCC and calcium carbonate.[27]

Improved flow properties

The co-processed excipient is reported to have better flow properties compared to its component or physical mixture by controlling the particle size distribution.[28] Good flowability is desired especially in the case of a high-speed rotary tablet machine. The Co-processing excipients show a significant role in improving the flow property of the powder mass ready for compression. A study showed that the co-processed Cellactose® has better flow than cellulose and lactose due to the spray drying technique used which resulted in particles of spherical shape and even surfaces.[29]

T.Sonica et.al showed that all the co-processed excipients prepared by granulation technique offered required flow properties. The flow was found to be excellent in the case of all co-processed excipients. The spray-dried product had a spherical shape and even surfaces, which also improved the flow properties.[30]

Clerch A. V. et al. proved the effectiveness of the combination of calcium phosphate dihydrate (brittle material) and microcrystalline cellulose (plastic material). Calcium phosphate exhibits good flow characteristics, high porosity, and hydrophilic behavior,

enabling fast disintegration; however, the tablets exhibit low breaking force and high friability in the final formulation. Owing to this brittle behavior, the combination using microcrystalline cellulose was prepared since this has good compatibility properties which compensate for the inadequate compression properties of calcium phosphate.[31]

For example, co-processed mannitol and calcium silicate.[32]

Fast disintegration

Fast disintegration is compendial and formulation requirement for immediate release and orally disintegrating dosage form. Co-processed adjuvants, by their high solubility, swelling, and wicking property, provide rapid disintegration to the developed formulation. For Example, **Rajashree Masareddy et. al. showed that** formulation of dispersible tablets of tizanidine HCl with good mechanical integrity and fast disintegration was successfully achieved using spray-dried excipient base of microcrystalline cellulose with SSL-hydroxypropyl cellulose.[33]

Cost-saving

Co-processed excipients are coming to the market frequently due to the less vigorous safety testing that is required for them. Since these are made of already defined and approved excipients, development is less taxing. The time required for approvals is less and the suppliers are more eager toward co-processed excipients as compared with the novel and new excipients. This also offers better functionality at a lower price.[36]

The manufacturer uses a single excipient with multiple functional properties, thereby reducing the number of excipients used and labour cost involved in their processing other than the direct compression method. The use of co-processed adjuvants simplifies the manufacturing process which leads to time and cost saving.[34]

Tablet Tensile Strength:

Co-Processed Particles is an Approach to Transform Poor Tableting Properties. Rahul Roopwani, Ira S. Buckner, investigate the role of co-processing in improving tablet mechanical properties. Gaba pectin has poor tableting properties, co-processed with methocel.

Co-processed gabapentin proved improvement in tablet tensile strength and strain rate sensitivity which was attributed to enhancing particle bonding.[35]

METHODS OF CO-PROCESSING:

1. Roller compaction

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

Faisal Al-Akaylehaet al, investigates co-processing lactose with synthetic amorphous magnesium silicate using roller compaction. The co-processed excipient demonstrated plastic behavior upon compression, good flowability and crushing strength, and a shorter disintegration time. Formulating this co-processed excipient with Mebeverine HCl and Losartan Potassium as model drugs, indicating its suitability as a single multi-functional excipient.[36]

Kothiya M. et al., developed co-processed excipients for fast dissolving tablets of Irbesartan by melt agglomeration technique. Lactose monohydrate and mannitol were selected as diluent and Polyethylene glycol 4000 was used as a binder. To improve the functionality of co-processed excipients 8 % crospovidone was incorporated.[37]

2. Wet granulation

Wet granulation is a conventional and simple method for co-processed adjuvant production. Fluid bed granulators and high-shear mixers are two commonly used equipment used for the same. In fluid bed granulation, the powder mix is subjected to fluidization by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed in the opposite direction to the airflow on the powder bed. The solid particles are mixed with the liquid droplets and hit the bed which results in adhesion and eventually the formation of granules. Partial drying by the fluidizing air occurs continuously during granulation.[38,39,40]

In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel. The binder solution is sprayed from the top. The development of large agglomerates is prevented by high shear force. With the new single-pot technology, drying occurs in the same

system. The granules formed are understandably denser than those obtained in fluid bedgranulation.[40,41]

R.Bennabas et.al. prepared co-processed excipients by wet granulation from Alginic acid and MCC. The obtained granules were characterized (tabletability, flowability, and disintegration time) and compared to the primary materials and a commercial multifunctional excipient, frequently used in the preparation of fast disintegrating tablets (Prosolv® ODT). It was found that the designed co-processed excipients present good tabletability, enhanced powder flowability in addition to a superior disintegration ability compared to the simple physical mixture and Prosolv® ODT. These performing functionalities were achieved accordingly to a synergistic effect obtained from the combination of both parent excipients (AA and MCC).[42] Gohel M. C. et al. prepared a novel co-processed excipient containing MCC, lactose, and DCP by wet granulation method using starch paste as a binder.[43]

3. Spray drying

Spray drying generally involves five steps: Concentration of feedstock, atomization, droplet-air contact, droplet drying, and separation and collection. The technique transforms a feed which might be a solution, suspension, or dispersion into dried particulate form by spraying it into a hot drying medium. The particle-particle bonding of excipients occurs during the process. The increased droplet surface area and high temperature cause the formation of spherical shape particles with improved flowability and suitable direct compression application such as Starlac.

This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. The feed can be a solution, suspension, dispersion, or emulsion. The dried product can be in the form of powders, granules, or agglomerates depending upon the physical and chemical properties of the feed, the dryer design, and final powder properties desired.[44]

Commercial Advantage:

- No need to maintain inventory of various excipients.
- Cost saving due to elimination of wet granulation production steps.
- Productivity increases due to increased machine speed.

• Cost saving in rework expenses.[43]

S. B. Shirsand et al**,** novel co-processed super disintegrants were developed by spray drying method using microcrystalline cellulose and mannitol in different ratios (1:1, 1:2, and 1:3) for use in the fast-dissolving tablet formulations. Co-processed super disintegrants prepared by spray drying method consisting of microcrystalline cellulose and mannitol exhibited good flow and compression characteristics. GLB tablets containing processed super disintegrants exhibited quick disintegration and improved drug dissolution.[45]

Chauhan SI, et al.used spray drying method for improving the compressibility of poorly compressible drugs. Etodolac was used as a model drug. Microcrystalline cellulose (MCC), lactose monohydrate (lactose), and StarCap 1500 (StarCap) were selected as components of the co-processed excipient. All the parameters were found to be within the acceptance criteria which concluded that the multifunctional directly compressible co-processed excipient was prepared successfully that improved the compressibility of the poorly compressible model drug etodolac along with spray drying as an efficient method for the preparation of co-processed excipient.[46]

Directly compressible co-processed excipients with improved functional property were developed using eudragit RSPO and ethyl celluloseNC50 without any chemical changes by the spray-drying method. Developed co-processed excipient showed good sustained drug release property and could be an alternate way to overcome the problems associated with a single polymer alone. The present studies successfully demonstrate the development of a novel co-processed free-flowing directly compressible polymer capable of providing anear zero-order release with minimum distortion of dosage form geometry.[47]

4. Hot-melt extrusion

Hot-melt extrusion uses heat with a temperature greater than 80°C. This method is not suitable for thermolabile materials. The excipients are melted and then pressurized through the die and solidify into a variety of shapes. The solvent is not required in the process as the molten polymer can function as a thermal binder.

Merits:

• Excellent repeatability.

• Complicate and intricate shapes are possible.

- Time required is less.

Demerits:

- Equipment and die cost high.

- Minimum economic length high.[48]

Giulia Loreti et.al. explore the potential of hot-melt extrusion (HME) for preparing hydroxypropyl cellulose (HPC)-based prolonged-release matrices intended for oral administration. In this respect, the formation of a composite material from ketoprofen and HPC, when mixed in specific ratios, was supposed to explain the differences observed between compressed and extruded systems in terms of morphological characteristics, hydration/swelling, and release. The obtained results support the possibility of exploiting the advantages offered by the HME technique, above all the potential for continuous manufacturing, in the preparation of prolonged-release swellable matrices based on a cellulose derivative.[48]Hetal Patel et.al prepare co-processed excipient core pellets (MOMLETS) that were developed by extrusion spheronization technique using Quality by Design (QbD) approach. BCS class II drug (telmisartan) was layered onto it in a fluidized bed processor. Co-processed excipient core pellets (MOMLETS) were successfully developed by QbD approach. Versatility, Industrial scalability, and simplicity are the main features of the proposed research.[49]

5. Melt granulation

The blends of excipients are mixed with a meltable binder (normally at solid-state below80˚C). The mixture is subjected to heat above the melting point of the binder with continuous blending to break the mass into agglomerates. The cooled agglomerates are finally screened to obtain granules with desired size.[50,51]Garget. al. co-processed dibasic calcium phosphate anhydrous with PEG 4000 and crospovidone, using melt granulation technique has resulted in a directly compressible vehicle with improved characteristics. The co-processed excipient proved to be superior in terms of flowability and compressibility. Aceclofenac tablets prepared using co-processed excipients showed better hardness, disintegration time and in vitro drug release in comparison to the Aceclofenac tablets prepared using the conventional wet granulation method.[52] Gohel M. C. et al., proved that melt granulation technique can be effectively used to prepare co-processed excipient. They

have prepared and evaluated lactose and microcrystalline cellulose-based, directly compressible adjuvant in which effect of percentage of polymer blend (PVP K 30 and PEG 4000; 5, 10, or 15%) and the polymer blend ratio (9:1, 1:1, or 1:9) were studied.[53]

6. Solvent evaporation

Solvent evaporation takes place in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent which is immiscible with the liquid manufacturing vehicle, followed by dissolving or dispersing the core excipient in the coating solution. Agitation force is applied to achieve the desired encapsulation size. Heat is used to evaporate the solvent.[54] Goyanes A. et al., prepared a co-processed MCC-Eudragit E excipient where acetone and isopropanol were used as solvents for Eudragit E. The wet mass was subsequently dried till organic solvents were evaporated.[55]Uppuluri P et al. prepared a co-processed excipient having corn starch and Sodium lauryl sulfate by two methods: solvent evaporation method and co-grinding method. He concluded that the solvent evaporation method with water as a solvent was the best suited for the preparation of co-processed excipients.[56]

Fast dissolving tablets of Febuxostat were prepared using a co-processed excipient employing direct compression technique to improve hardness, reduce disintegration time as well as achieve a better dissolution rate as compared to the commercially available formulation. A co-processed excipient of crospovidone and microcrystalline cellulose PH 102 in a 1:1 ratio was prepared by the solvent evaporation technique The tablets were prepared by direct compression technique with the application of a 32 randomized full factorial design. The prepared tablets were able to release more than 80% of the drug within 10 minutes of the start of dissolution testing and were able to show a better drug release profile in comparison to available marketed formulation.[57]

7. Freeze-thawing:

It is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compatibility of the excipients. Patel S. et al., combined mannitol with cellulose by the freeze-thawing process.[58]

Examples of Marketed Co-processed excipients:

1. **Microcrystalline Cellulose–Starch**

Trade name - Not recognized.

Composition - Formation of dispersion of maize-starch and solution of MCC separately. Addition of starch dispersion into MCC solution adjusting pH of the mixture followed by spray drying to produce micro-particles.

Characteristics - A new polymer type was generated from the pH and temperature-controlled hybridization effected by mixing colloidal dispersions of MCC and Maize-starch. A more efficient multifunctional excipient in terms of disintegration efficiency and loading capacity for the formulation of oral tablets for rapid release of APIs by direct compression process along with other enhanced physic-mechanical properties is obtained.

2. **Microcrystalline Cellulose-Mannitol**

Trade name- Avicel HFE 102

Composition - Co-processing of 90% Avicel PH102 and 10% mannitol.

Characteristics - Flow properties of Avicel HFE102 are significantly better than those of Avicel PH 102. The Avicel HFE 102 exhibits better tabletability at a slower tableting speed, especially when lubricated. Avicel HFE 102 is also less sensitive to lubrication.[59]

3. **Pregelatinized Starch**

Trade name - Insta starch / Lycatab / Sepistab

Composition - By heating aqueous slurry containing up to 42% w/w of starch at 62-720C, having additives such as gelatinization aid (salt or bases) and surfactants. Then they are spray-dried, roll-dried, or drum-dried.

Characteristics - As binder-diluent in oral capsule and tablet. Having enhanced flow and compression characteristics. Tablet-binder in dry compression.[60]

4. **Copovidone**

Trade name - Kollidon VA 64/Plasdone S 630.

Composition - Copovidone is a linear random copolymer based on N-vinyl-2 pyrrolidone and vinyl acetate in the ratio of 6:4 by mass.

Characteristics - Copovidone is a white/yellow-white with fine particle size and excellent flow properties. Dry Binder in Tablets (Direct compression), Binder in Tablets, Pellets & Granules (Wet Granulation), Dry Binder in Granules (Roller Compaction), and Film Former for tablet Film Coating & Sugar Coating, Film Former for Subcoating Tablets and Matrix Former for Melt-Extrusion for tablets.

5. **Lactose–Cellulose Trade name - Cellactose.**

Composition - co-processed α-lactose and cellulose.

Characteristics - improved flow property and high dilution potential along with excellent binding properties.

6. **Lactose-Microcrystalline Cellulose**

Trade name - Microcelac 100

Composition - A co-processed spray-dried filler/binder for direct compression and composed of 75% w/w a-lactose monohydrate and 25% w/w microcrystalline cellulose.

Characteristics - Superior flowability and binding properties compared to physical mixtures of microcrystalline cellulose with different lactose grades e.g., α-lactose monohydrate (lactose 100 M), anhydrous βlactose (Pharmatose DCL21), and spray dried lactose (Pharmatose DCL11). It also shows the least lubricant sensitivity.[60]

7. **Lactose-Maize Starch**

Trade name – Starlac

Composition - A co-processed spray-dried filler/binder for direct compression and composed of α-lactose monohydrate and Maize-starch.

Characteristics - The new product should combine the good flowability and plastic deformation of spray-dried lactose with the elastic deformation and rapid disintegration of native maize starch. StarLac demonstrated good compatibility and release behavior. It exhibited deformation behavior with higher parts of plastic and elastic deformation than FlowLac, therefore Starlac is of interest for the manufacture of pressure-sensitive drugs. The

advantage of Starlacis its good flowability depending on the spray-drying process, an acceptable crushing force due to its lactose content, its rapid disintegration depending on starch. Gohel and Jogani demonstrated the use of multiple linear regression in the development of co-processed lactose and starch. The authors concluded that as the lactose/starch ratio increased Carr's index of the adjuvant and crushing strength of the tablets increased while friability decreased. The percentage of starch paste has an inverse effect on friability.

8. **MCC-Sodium Carboxymethyl Cellulose**

Trade name - Avicel CL-611

Composition - Co-processed MCC and sodium carboxymethyl cellulose via the co-drying process.

Characteristics - Impart a thixotropic viscosity profile, and increase formulation stability across a wide range of pH. Used as a stabilizer.

9. **Mannitol-Povidone Trade name - Ludiflash.**

Composition - Coprocesed blend of 90% Mannitol, 5% Kollidon CL-SF (Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate).

Characteristics - Specially designed for directly compressible, high-speed tableting, and hard tablets with very low friability. Ludiflash has good flowability, less water absorption, and no segregation of the active ingredients.

10. **Orocell**

Trade name - Orocell 200 & Orocell 400**.**

Composition - Spheronised mannitol with different particle sizes.

Orocell 200 with 90% mannitol

Orocell 400 with 90% mannitol

Characteristics - A developed filler-binder with high dilution potential and good disintegrating property useful for orally disintegrating tablets.

Limitation of Co-Processed Excipients:

Although co-processed excipient shows a list of promising benefits, however, there are few drawbacks in using co-processed adjuvants. Co-processed adjuvant is available as pre-mixed at a fixed ratio of an individual constituent. The user has no freedom to alternate the ratio of the excipient.[61] Moreover, co-processed adjuvant lacks the official acceptance in the pharmacopeia.[62] For this reason, a co-processed adjuvant is not accepted by the pharmaceutical industry unless it exhibits significant advantages in tablet compaction when compared to the physical mixtures of the excipients.[63]

Current and Future Status of Co-Process/ Added Functionality Excipients:

At present co-processed excipients have less applicability in the pharmaceutical industry but surely these will be utilized with enhanced functional properties at low concentrations in the future. Very few new chemical entities are being introduced in the market due to stringent rules and regulations by consider safety, efficacy, and cost. Also, very few improvements in existing excipients will help in increased use of co-processed excipients in the coming future. Uprising technologies and much more modification are implemented daily in the pharmaceutical industry to achieve a high production rate. The growing popularity of high functionality excipients counterpart tablet machine increasing speed capabilities, to modulate the permeability, solubility, or stability of the drug, increasing performance expectations related to disintegration, dissolution, bioavailability, etc. makes a fantastic opportunity for the development of novel drug delivery system.

CONCLUSION:

There is no single-component excipient that fulfills all the requisite performance to allow an active pharmaceutical ingredient to be formulated into a specific dosage form. Co-processed excipient has received much more attention in the formulation development of various dosage forms, especially for tablet preparation by direct compression method. We observe the shift in tableting toward direct-compression and high-speed manufacturing has forced the excipient industry to search for new excipients. Co-processing is a novel concept of combining two or more excipients that possess specific advantages that cannot be achieved using a physical admixture of the same combination of excipients. With advantages offered by the upcoming newer combination of excipients and newer methods of co-processing, co-processed excipients are for sure going to gain attraction both from academia and the

pharmaceutical industry. Furthermore, it opens the opportunity for the development and use of a single multifunctional excipient rather than multiple excipients in the formulation. A better understanding of the manufacturing variables and market demand has led to the development of specific excipients that enhance the efficiency of pharmaceutical formulations.

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