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REVIEW ON NOVEL PHARMACEUTICAL CO-PROCESSED EXCIPIENTS

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ABSTRACT

When creating a dosage form, excipients are crucial. Scientists studying drug formulation have realized in recent years that single component excipients don't always perform well enough to enable the proper formulation or manufacturing of specific active pharmaceutical ingredients. Moreover, creating new chemical excipients with better qualities comes at a hefty price. New combinations of current excipients are an intriguing possibility for enhancing excipient functioning these days, given the volume of combination excipients that excipient makers have brought to the commercial market. Through subparticle alterations, particle engineering of individual excipients and excipient combinations through coprocessing has offered an alluring tool for creating high functionality excipients that are appropriate for contemporary tablet manufacturing procedures. Excipients that are coprocessed are a mixture of two or more excipients intended to combine physically without undergoing substantial chemical change, these Compared to individual excipients, coprocessed excipients offer higher functionalities, such as improved flow properties, compressibility, and decreased lubricant sensitivity. All of the developed coprocessed excipients are listed, emphasizing their many useful and multifunctional qualities. Additionally covered are regulatory concerns pertaining to the creation of novel excipients and coprocessed excipients. These excipients include the following: granulation/agglomeration process, solvent evaporation, speronization, melt extrusion, flow ability, and compressibility. Promoted. Products like Ludipress, Celactose, and Prosolv, among others, have previously demonstrated their value in the market by lowering the product's cost and the amount of excipients while preserving the formulation's effectiveness. However, these excipients have certain drawbacks because of their quality evaluation and reproducibility of the result.

Keywords: Excipients, Method Of Excipient, Novel Excipients, API.

I. INTRODUCTION

Substances other than the API which have been appropriately evaluated for safety and are purposefully included in a drug delivery system" is how the International Pharmaceutical Excipients Council (IPEC) defines an excipient. Excipients, for instance, can

1. Participate in the drug delivery system's manufacturing process
2. Safeguard, uphold, or improve patient stability, bioavailability, or acceptability,
3. Aid in identifying the product, or
4. Improve any additional aspect of the drug's general safety, efficacy, or delivery when it is being used or stored.[1]

Excipients are solvents that are employed to make a dosage form but are not included in the finished product; hence, granulation fluids that may be dried off later must adhere to applicable pharmacopoeia regulations unless they are sufficiently justified. The original idea of "inactive support" is no longer maintained by excipients due to their impact on both biopharmaceutical and technological components. Functionality is the desired activity, the excipient's counterpart of the efficacy of the active ingredient. An excipient's functioning is one of its fundamental characteristics. Since excipients are often made in batches, variations may occur from batch to batch from the same manufacturer. Excipients derived from various sources can not have the same characteristics when it comes to usage ina particular formulation. Users may want to ascertain equivalency in

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final performance or identify such features before to usage in order to ensure interchangeability in such situations. Thus, these tests pertain to the functionality that an excipient adds to a particular formulation.[2]

The pharmaceutical industry constantly evolves to meet growing demands for efficiency, cost reduction, and innovation in drug development. A novel co-process in this domain involves combining two or more existing manufacturing techniques, such as granulation, blending, or coating, to enhance drug quality, stability, and scalability. These processes aim to optimize the production pipeline while ensuring compliance with stringent regulatory standards. For example, a co-processed excipient approach, where multiple excipients are combined in a single process, has gained significant attention for improving tablet formulations and drug delivery systems.

II. TYPES OF EXCIPIENTS

- Single entity excipients.
- Mixtures/blends of multiple excipients.
- Novel excipients organization.
- Co-process excipients.

2.1 Single entity excipients

Excipients that only contain one primary component are referred to as single entity excipients. [8]

- Related elements.
- The aids of residual processing.
- Supplements.

2.2 Mixtures or blends of multiple excipients

Low to medium shear processes are used to create simple physical mixtures of two or compendial or non-compendial excipients. In these mixtures, the individual components are mixed together without undergoing significant chemical changes, but in solid mixtures or blends, the individual excipients remain physically separate at the particulate level.[9]

2.3 Novel excipients or new chemical entities

It is characterized as excipients that undergo chemical modification to create new or innovative excipients; these are typically not included in the FDA's database of inactive ingredients. The term "new excipient" refers to any inactive component purposefully included in medicinal and diagnostic products.[9]

2.4 Co-process excipients

A variety of co-processing techniques are used in the development of pharmaceutical formulations, including spray drying, solvent evaporation, crystallization, melt extrusion, and granulation/agglomeration. Co-process excipients are combinations of two or more compendia or non-compendia excipients intended to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change.[9]

Combining two or more compendial or non-compendial excipients to physically alter their characteristics in a way that cannot be accomplished by straightforward physical mixing and without causing a substantial chemical change is known as co-processing. It is possible to employ a wide range of co-processing techniques, including common unit operations like granulation, spray drying, melt extrusion, milling, etc. The materials utilized, their form (such as liquid or dry powders), and the particular physical qualities required will all influence the decision for a given application. Similarly, based on the intended performance, the component ratios may change. [9]

Advantages of co-processed excipients

- Regulating the ideal particle size and size distribution to improve flow characteristics.
- Increased lubricant sensitivity, flow characteristics, fill weight volatility, compressibility, and dilution potential.
- It can be also improving the tablet hardness and decrease disintegration time.[10]

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III. PRINCIPLE INVOLVED IN CO-PROCESSING

The molecular, particle, and bulk levels are the three solid state levels that define solid substances. Since changes at one level have an impact on another, these levels are intimately related to one another.[11] The arrangement of individual molecules in the crystal lattice makes up the molecular level, which also encompasses amorphous states, polymorphism, and pseudo-polymorphism. Individual particle characteristics, including size, shape, porosity, and surface area, are included at the particle level.[12-13] An ensemble of particles and characteristics, including flow ability, compressibility, and dilution potential, make up the bulk level and are crucial to excipient performance.The different solid state levels are depicted in Figurel, along with the effects of changes at one level on the others. The scientific foundation for creating new grades of current excipients and novel combinations of current excipients is provided by this interdependency among the levels.[14] Excipient capabilities including flowability, compactability, dilution potential, disintegration potential, and lubrication potential are influenced by the basic solid state characteristics of the particles, including morphology, particle size, shape, surface area, porosity, and density. Therefore, designing a particle that can provide the required capabilities must be the first step in creating a new excipient. However, only a little amount of functionality enhancement can be achieved by particle engineering a single excipient.

Numerous opportunities to create custom "designer excipients" to meet certain functionality needs are ensured by the abundance of excipients available for coprocessing.[15]

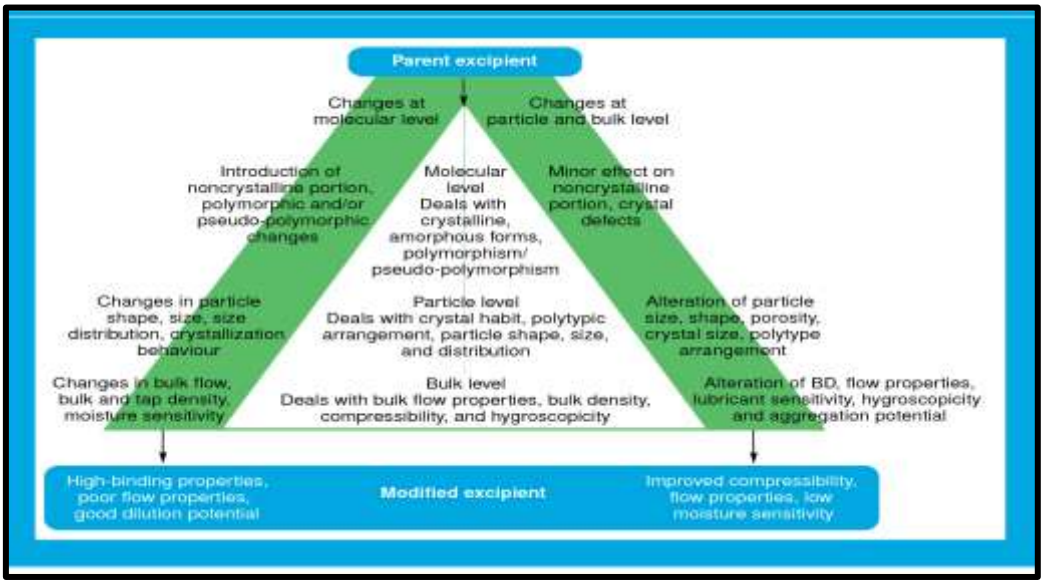

Figure 1: International journal of pharmaceutical and chemical sciences

IV. METHODOLOGY OF CO-PROCESSING

4.1. Spray drying.

4.2 Solvent evaporation.

4.3 Crystallization.

4.4 Melt extrusion.

4.5 Granulation/Agglomeration.

4.1 Spray drying

Allow can be transformed from a fluid state into dried particles using this spray drying technology. Depending on the physical and chemical characteristics of the feed and the dryer design, the final powder attributes needed can determine whether the dried product is in the form of powders, granules, or agglomerates. The feed can be a solution, suspension, dispersion, or emulsion. Spray drying is a continuous particle processing and drying operation. It can help design particles with desired properties by adjusting parameters such as inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in feed, and disc speed. Therefore, the four-step spray drying procedure can be desired.[23]

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- Liquid atomization into droplets.
- The droplet's interaction with the heated drying gas.
- The droplets quickly evaporate to produce dry particles.
- Makes use a cyclone to recover the dry particles from the drying gas.

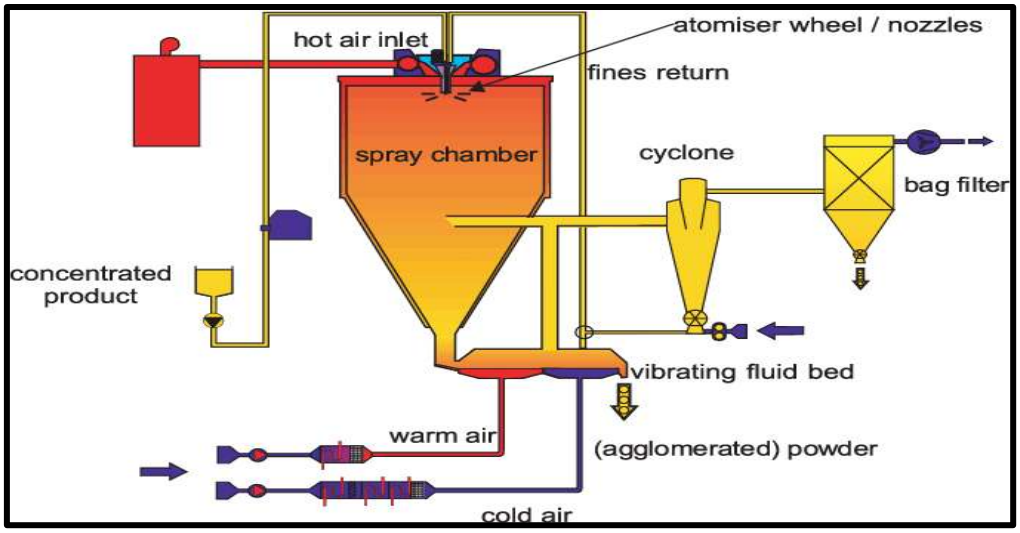

Figure 2: Spray Drying Process.

Advantages of spray drying

- The potential for related non-missible items to run continuously.
- It enables the simultaneous blending and drying of both soluble and insoluble compounds.
- Allows for the protection and repair of sensitive active compounds on natural carriers.
- Increases compressibility and hardness.
- Reduces disintegration time and increases machine tableting speed.

4.2 Solvent evaporation

The liquid manufacturing vehicle is used to carry out the procedure. A volatile solvent that is incompatible with the liquid production vehicle phase dissolves the coating excipient. The coated polymer solution is agitated to dissolve or distribute the core excipient substance to be microencapsulated. To create the right size microcapsule, the core coating material mixture is distributed during the liquid manufacturing vehicle phase. After heating the combination until it evaporates, the liquid vehicle temperature is lowered to room temperature while stirring continuously.Microcapsules can now be isolated as powders, coated onto surfaces, or employed in suspension form. Either water-soluble or water-insoluble materials could make up the main components. [24]

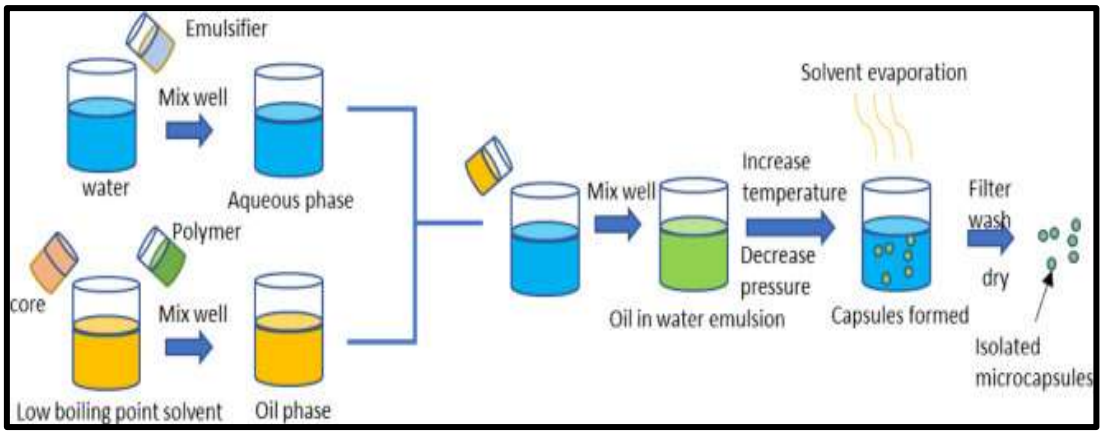

Figure 3: The process and mechanism of solvent evaporation technique.

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4.3 Crystallization

The process of solid crystals forming naturally or artificially through melting, precipitation, or, less frequently, direct deposition from a gas is known as crystallization. The solution needs to be supersaturated in order for crystallization to happen. This implies that there must be more dissolved solute entities (molecules or ions) in the solution than there would be in the equilibrium (saturated solution). There are several ways to accomplish this, but the most popular ones in industrial practice are (1) chilling the solution, (2) adding a second solvent to make the solute less soluble (a process called drown-out or antisolvent), (3) chemical reaction, and (4) pH change. Sugar Tab [Sucrose, Invert sugar] is one example. [23-25]

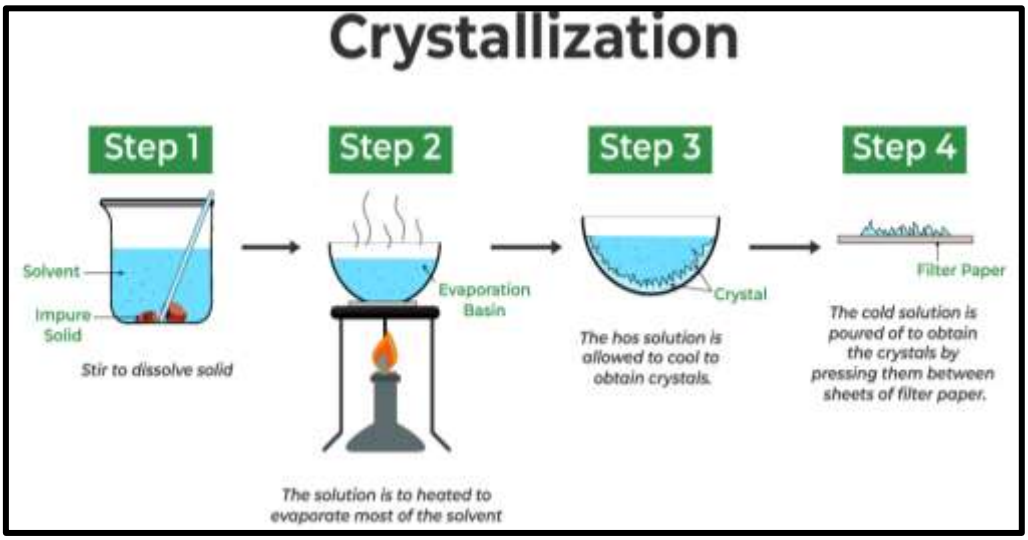

Figure 4: Crystallization.

4.4 Melt extrusion

Melt extrusion is the process of using a molten substance that has been extruded via an extruder to create tiny beads or pellets. Four separate components make up extruders. [26]

1. A hopper that holds the materials to be extruded may be present through the hole through which material enters the barrel.
2. The barrel and the screws that move and, if necessary, mix the material make up the conveying (process) part.
3. A hole (die) through which the material is shaped as it exits the extruder.
4. Auxiliary downstream equipment for collecting, cutting, and/or cooling the final product. Compressol S [Mannitol, Sorbitol] [23-25] is one example.

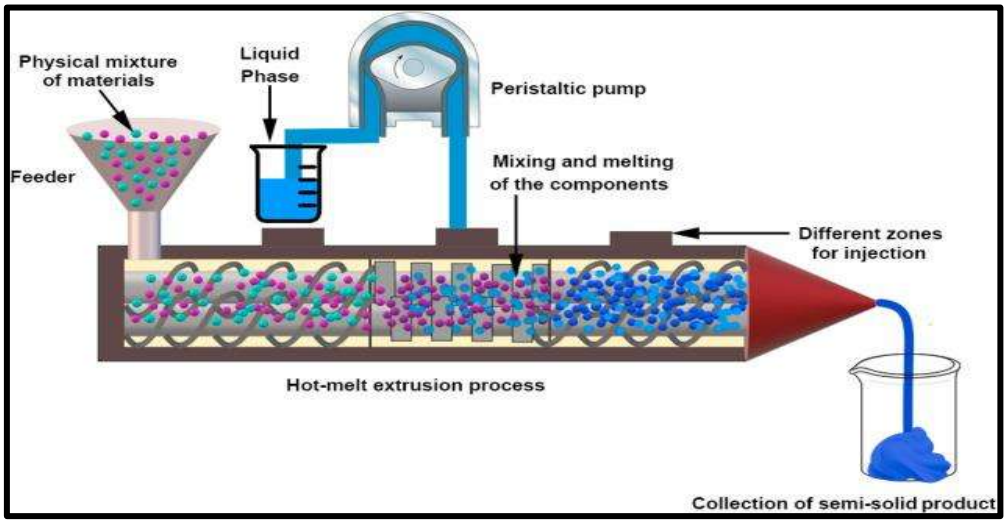

Figure 5: Melt Extrusion Process

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Advantages

- Outstanding repeatability.
- It is possible to create complicated and complex shapes.
- It takes less time.

Disadvantages

- Die and equipment are expensive.
- Highest minimum economic length. [27]

4.5 Granulation/agglomeration

The formation or crystallization of grains is known as granulation. Depending on their intended purpose, granules can range in size from 0.2 to 4.0 mm. "Agglomeration" is a synonym for granulation. Agglomeration techniques, or more broadly, technologies that increase the size of particles, are excellent means of altering the characteristics of products. Powder agglomeration is frequently utilized to enhance physical characteristics such as bulk density, flowability, wettability, and product appearance.[28]

Advantages

- Water or any other solvent is no longer needed.
- Quick processing time.
- It may work well with traditional equipment.[29]

V. CO-PROCESSED EXCIPINENTS

Combining two or more compendial or non-compendial excipients to physically alter their characteristics in a way that cannot be accomplished by mere physical mixing without causing a substantial chemical change is known as co-processing. However, in certain cases, such as in-situ salt production, the essential components may form. A wide range of co-processing techniques can be applied, including common unit operations including milling, melt extrusion, spray drying, and granulation. The materials utilized, their form (such as liquid or dry powders), and the particular physical qualities required will all influence the decision for a given application.[30]

Using techniques like co-drying, coprocessed excipients are made by integrating one excipient into the particle structure of another excipient. They are therefore basic physical combinations of two or more excipients that are already in use combined at the particle level. In comparison to physical mixes of components or individual components, coprocessing excipients results in the creation of excipient granulates with improved characteristics. With filler-binder combinations being the most often tested, they were designed mainly to address the problems of flowability, compressibility, and disintegration potential. The selected excipient combination should work in concert to conceal the unfavorable characteristics of each excipient while maintaining or enhancing the excipients' desired qualities.For instance, if a filler-binder material has poor disintegration qualities, it can be coprocessed with another excipient that has high porosity and good wetting qualities. This will increase the amount of water ingested, which will help and accelerate the tablets' disintegration. Combining two or more well-known excipients using the proper procedure is one definition of it. In contrast to the basic physical mixes of the components, co-processing excipients may result in the creation of excipients with better qualities. Getting a product with extra value based on its functionality/price ratio is the primary goal of co-processing.[31]

The first step in creating a co-processed directly compressible adjuvant is choosing which excipients to mix, their desired ratio,choosing a preparation technique to minimize batch-to-batch fluctuations and obtain an optimum product with the required physico-chemical characteristics. To create an integrated product that is more functional than a simple mixture of components, the right amount of a functional element must be paired with an excipient that is reasonably priced.

Co-processing is intriguing since it modifies the products' physical characteristics without changing their chemical makeup. The components are embedded within minigranules to provide a fixed and uniform distribution. The actives' adherence to the porous particles reduces segregation, which facilitates simple and

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dependable process validation and management. The components' anisotropic behavior is reduced by their randomized embedding in unique minigranules. Therefore, during the compaction process, several clean surfaces are created and deformation can occur along any plane. Therefore, the benefits of both direct compression and wet granulation are combined when the co-processed excipient is used.If the functions of the one-body components are more potent than those of the dry blend of components made via gravity combination, then the employment of one-body components is justified. The tablet's quality should be improved uniformly by this synergistic impact in all areas, from stability to dissolving and/or hardness. In co-processing, excipient mixes are created to utilize each component's benefits and get around any particular drawbacks. The most crucial qualities are the co-processed excipients' blending and binding capabilities, which must outperform a physical mixing of the initial ingredients. Another consideration when choosing a co-processed product is cost.[32]

Because one excipient is just insufficient, combinations of excipients are often needed to achieve certain features of a pharmaceutical formulation. Therefore, it is conceivable to combine several well-known materials to create new and/or better physical properties; consequently, they work in concert. However, in this case, the performance of the excipient formulation cannot be achieved by simple physical mixing. Two or more compendial excipients that have undergone only minor chemical alteration during formulation make up these so-called "coprocessed" excipients .Consequently, the safety profile of a coprocessed excipient is frequently identical to that of a corresponding physical mixture. Common production methods include spray formulation, mixer granulation, fluid bed granulation, and microencapsulation. The manufacturing of pharmaceutical products is often facilitated by coprocessed excipients. Their use can reduce production costs since it improves process efficiency and reduces the requirement for testing and documentation because fewer excipients are used. They even allow the reduction of the number of production stages needed to manufacture a dosage form when appropriate. They are widely used in direct compression and coating applications, which speed up and simplify the creation of novel medications and their production .

Table 1: lists a few instances of commercially available co-processed excipients. [33,34,35]

COPROCESS EXCIPIENT	TRADE NAME	ADDED ADVANTAGES
Lactose 3.2% Kollidon 30, Kollidon KL	Ludipress	Low degree of Hygroscopicity, good flowability, tablet hardness independent of machine speed
Lactose 25% cellulose	Cellactose	High compressibility, good mouthfeed, better tableting at low cost.
Microcrystalline cellulose, silicone dioxide	Prosolv	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability
Microcrystalline cellulose, guar gum	Avicel CE 15	Less gritiness, reduced tooth packing, minimal chalkiness,creamier mouth feed, improved overall palatability.
Calcium carbonate, Sorbitol	FormaXX	Controlled particle size distribution
Microcrytal line cellulose, lactose	Microcelac	Capable of formulating high dose, small tablet with poorly flowable active good flow.

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90%Microcrystalline cellulose, 10% mannitol	Avicel HFE 102	Better Flow properties, better tabletability at slower speed
Microcrystalline carboxy methyl Cellulose	Avicel CL 611	Impart a thixotrophic viscosity profile, increase formulation stability across a wide range of PH use as stabilizer
Starch w/w, gelatinisation aid & Surfactant	Pregelatinised starch	Binder, diluent in oral capsule and tablet. having enhance flow and compression characteristics. Tablet binder in dry compression.
a-lactose monohydrate & ß cyclodextrin	Not recognised	Good flowability, compressibility & compactibility. limitations of ß cyclodextrin for it flowability & lubrication sensitivity is overcome.
Lactose, Polyvinylpyrolidone	Crosspovidone / Ludipress	An excellent filler binder with very high dilution potential & good binding property.
HPMC, lactose	Not recognised	Improve flowability, & compressibility
Sucrose, 3% Dextrin	Dipac	Use for direct compressible tablet, improve flowability.
Sucrose 3% dextrin, Microcrystalline cellulose, Silicon Dioxidel	Dipacprosolv	Directly compressible, better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability.
95% ß lactose, 5% lactitol	Pharmatose dcl 40	High compressibility
Orocell 200 with 90% mannitol Orocell 400 with 90% mannitol	Orocell 200 & orocell 400	A development filler binder with high dilution potential and good disintegrating property useful for oral disintigrating tablet
Microcryatalline cellulose 89%, hidroxypropylmethyl cellulose2%, & crosspovidone 9%	PanExcea MMC200G	Strong intraparticle bonding bridges between the components, improved the blending, rapid disintegration time.
I-O-Dglucopyranosyl,6-0-D glucopyranosyl D-sorbitol (1:3) particle size 90%,50%.	Isomalt galen IQ-721	Highly soluble agglomerated spherical isomer for fast dissolving and fast disintegration time
Mannitol 84% crosspovidone 16% silicon dioxide < 1%	Pharmacetical MCL	High compactibility, high loading in small diameter tablets, smooth mouth feel, rapid disintegration time

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Matheirnnitol particle size 60%	Manogem™™ EZ	Assist in formulating difficult to use non hygroscopic orodispersible tablet containing find drug

Limitation of co-processed Excipient

One of the main drawbacks of co-processed excipient mixtures is that ratio is set. When creating a novel formulation, this preset ratio might not be the best option for the API and the dosage per tablet being developed. Pharmacopoeia does not formally recognize co-processed adjuvant. Because of this, the pharmaceutical mixtures of the excipients will not accept a combination filler binder. Despite being recognized USP/NF products, compressible sugar and spray-crystallized dextrose-maltose (Emdex) are co-processed products as separate components.[36]

VI. RESULT

The implementation of novel co-processed excipients has shown remarkable improvements in pharmaceutical formulations. The key results observed include:

1. Improved Flow Properties

Co-processed excipients, such as those combining microcrystalline cellulose (MCC) and colloidal silicon dioxide, exhibit superior flowability compared to their individual components. This improvement facilitates efficient tablet manufacturing by reducing sticking and ensuring uniform die filling during compression.

2. Enhanced Compressibility

Co-processed excipients, like Prosolv®, demonstrate better compressibility and hardness than their single counterparts. This eliminates the need for additional binders and reduces tablet weight variations, making them ideal for direct compression methods.

3. Increased Drug Stability

By combining ingredients with synergistic effects, co-processed excipients protect sensitive APIs (active pharmaceutical ingredients) from environmental factors like moisture and oxidation. This enhances the shelf life of the final product.

4. Optimized Drug Release

Profiles: Certain co-processed excipients, such as those combining lactose and polymers, can modify drug release rates, enabling the formulation of controlled or sustained-release dosage forms.

5. Simplified Manufacturing Process

The use of co-processed excipients reduces the number of processing steps, such as granulation or milling, by integrating multiple functional properties in one product. This leads to shorter production times and lower costs.

6. Regulatory Acceptance:

Co-processed excipients are increasingly being accepted by regulatory agencies like the FDA, especially when they conform to quality-by-design (QbD) principles.

VII. CONCLUSION

Novel pharmaceutical co-processes are pivotal for advancing drug manufacturing, ensuring high-quality products, and meeting the demands of modern healthcare systems. By addressing industry challenges such as cost, efficiency, and sustainability, these innovations promise to revolutionize the pharmaceutical landscape. The advantages include enhanced efficiency, reduced costs, and improved drug performance, which align with modern quality and sustainability goals. Moreover, these excipients offer flexibility for formulators, enabling the development of innovative drug delivery systems, such as orally disintegrating tablets (ODTs) and controlled-release formulations. Future research in this field should focus on exploring novel combinations of excipients tailored for specific therapeutic needs, such as poorly water-soluble APIs or biologics. Additionally, advancements in co-processing techniques, such as 3D printing and nanotechnology, could further expand the utility and functionality of these materials.One of the main barriers to coprocessed excipients' commercial

success is that they have not yet been included in official monographs. Any pharmaceutical coprocessed excipient's ability to work, be safe, and be of high quality will determine its success. Because coprocessed excipients improve functionality by getting around the drawbacks of single excipients, their use is growing. Coprocessed excipients have a lot of room to grow as novel chemical entities are developed on a daily basis.Safety evaluation is necessary for the development of new excipients, and it takes time and money. Coprocessing already-approved excipients will lower the safety evaluation rather than creating a new one. IPEC to lower regulatory uncertainty, co-processed excipients should be evaluated using the New Excipient Safety Evaluation Procedure.

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