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Review Article

Advances in Co-Processed Excipients: Multifunctional Platforms for Diverse Pharmaceutical Formulations

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ABSTRACT

As it adds so many advantages to the finished formulations, excipient utilised in pharmaceutical dosage forms is a special and important ingredient that is just as important as the API. Improving API absorption and bioavailability, boosting organoleptic characteristics and filling the entire tablet are among the benefits. Nevertheless, choosing the right excipients remain taxing due to matters including the various attributes of excipients, incompatibility between API and excipient, moisture absorption capacity, surface acidity, crystal nature and production of hazardous excipients that are inferior, among other issues. The substantial toxicity of the excipient may have a significant effect on the pharmacokinetic and pharmacodynamic properties of the API and its dosage form. It can be the result of utilising several excipients that perform inconsistently. The pharmaceutical sector can address its excipient-related problems by embracing and enforcing cGMP, but this won't stop the production process from being affected by the long, costly and laborious regulatory procedure. Co-processed excipients have multiple uses, thus when creating dosage forms, they might give formulation scientists something unique. An alternative and potential method for choosing and utilising an ideal combination of currently available excipients over the conventional excipients in the preparation of dosage forms is made possible by the need for co-processed excipients, the need for excipients to be co-processed, development techniques, risk and valuation studies, use and compliance with standards.

Keywords: Co-Processed excipients, Pharmaceutical Formulations, Wet granulation, Manufacturing methods.

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INTRODUCTION

Pharmaceutical excipients are components or mixtures of substances that are used in a variety of ways as carriers or vehicles to give various types of dosage forms consistency, volume and uniformity. The important qualities of excipient are demonstrated throughout the entire process, from first weighing and continuing through manufacture and patient administration.[1,2] Excipients are defined by the International Pharmaceutical Excipients Council (IPEC), the United States Food and Drug Administration (USFDA) and the United States Pharmacopoeia (USP) as non-pharmacological substances that are found in significant quantities in finished formulations but not considered Active Pharmaceutical Ingredients (API). Excipients' inert nature reveals their multipurpose utility.[3]

Conventional dosage forms, including pills, creams, pastes, capsules and ointments, employ excipients as diluents, fillers, colouring, flavouring and preserving agents. The poor dissolution, permeation and bioavailability of some drugs from the Biopharmaceutical Classification System (BSC) have recently been found to be enhanced or improved by the use of excipients in advanced dosages as solubility and absorption enhancers,[4,5] emulsifying agents,[6] wetting agents[7] and release modifiers.[8,9] Pharmaceutical excipients are recognised as distinct and important compounds with equal relevance as the API in the end-product formulations because of their inert and many advantages.[10] Excipients are typically added in greater amounts (1 to 99%) compared to API in dosage formulations. The excipients incorporated in the finished products in the range mentioned above serve a variety of purposes for the API, including filling the entire volume/weight of the ultimate dosage forms, reducing deterioration of the API to regulate its stability, improving accuracy of the API amounts in the finished product, improving the API's absorption and bioavailability, boosting the organoleptic features (taste, colour and odour) and, lastly, promoting patient compliance and acceptance. Excipient also makes the finished product more elegant, making it appropriate for patient administration through a variety of ways.

In addition to this, the safety and efficacy of the excipient are also very important and are positively correlated with the various functions of excipients.[11-13] Excipients originate from a multiplicity

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of sources, comprising biological, chemical, mineral and animal processes. What matters most is that they are safe, efficacious and compatible with the API in dosage forms. Pharmaceutical technology has recently made important strides that have shown how to evaluate the safety, efficacy and combining behaviour of excipients to API and excipients to excipients in a straightforward and efficient manner.[14] Consequently, the end product and its acceptance by the patient is influenced by excipients, their preparation and the choice of excipient when it comes to API.

Excipient selection is crucial in formulation development because well-performing excipients have demonstrated improved compatibility with Active Pharmaceutical Ingredients (APIs). The formulation scientist receives final approval to manufacture specified dosage forms based on the excipients' compliance with the API.[15] However, because excipients come in a variety of forms, including solid, liquid, semi-solid and gaseous, choosing the right ones for the API is challenging. The physicochemical characteristics of these excipients, such as their capacity to absorb moisture, studies of acid-base interactions, their surface acidity, the development of defects on their surface, their crystallinity and the existence of any products from oxidative reactions, are also examined. Furthermore, during the production process, there exists a potential risk of producing substandard items with elevated levels of toxicity. The use of several excipients and the incompatibility of some excipients with API may be the cause of the toxicity in the excipients. When an excipient loses its inert character, it combines with the API to produce unwanted harmful compounds. This is known as excipient toxicity. The pharmacokinetic and pharmacodynamic characteristics of the API in the formulation have probably been altered by the hazardous excipients.[16]

The excipient toxicity problems have been resolved by embracing and using the current Good Manufacturing Processes (cGMP) as have been put in place for API. This strategy might, however, have an impact on the formulation scientist in excipient production process because it would take longer, cost more and-above all-need permission from multiple regulatory bodies. Collecting, extracting, chemical synthesis, buildup, particle size reduction and fermentation are some of the steps involved in the multi-step process of excipient manufacture. The new excipient is frequently created as a continual or batch process by combining these different stages.

Similar to API, the newly designed excipient is expensive and subject to an arduous regulatory evaluation procedure. The evaluation procedure is specifically designed to evaluate the excipient's quality, safety, efficacy and functionality.[17]

The results for every excipient, old and new, have been kept up to date by the USFDA and are stored in a database called "Inactive Ingredients (IIG)." Furthermore, the sanctioned excipient is recognized as "GRAS," or "Generally Regarded as Safe." The producer can choose excipients that are desirable and complementary with the API to formulate appropriate dosage forms with the use of the IIG database. Development cost of the excipient is increased when several phases are involved, which additionally impacts the excipient of choice and application in the formulation. Without a pharmaceutical excipient, a pharmaceutical dosage form cannot be viable because, aside from API, the pharmaceutical excipient is frequently necessary for the formulation to work.[18,19] Moreover, it has been noted that a basic physical mixture including one or two excipients is unable to yield the multifaceted excipient required for solid dosage forms.[20] Pellets, granules, capsules and tablets are examples of concrete oral dosage forms. These forms account for over 70% of all pharmaceutical preparations and are still regarded as one of the best as they provide both the patient and the formulator with a number of advantages.

This advantage comprises easy and affordable preparation techniques, optimal administration, convenience of packaging, transporting and dispensing, precise dosage administration, compactness and strong stability. Particularly, the excipients of tablets determine their numerous advantages.[21] Higher quantities and higher amounts of pharmaceutical excipients are present in between 70 and 80 percent of pharmacological dosage forms.[22] Increased excipient content probably has an impact on the tablet's processing capability and functional characteristics.[23] The Direct Compression Technique (DCM), which involves simply the preparation and subsequent compression of a dry mix of API and excipient utilizing a tablet compression machine, is the single most effective approach for tablet production when as opposed to wet and dry granulation. In addition, DCM has several advantages, such as fewer bacterial contamination,[24] one to two process stages, enhanced dynamic dissolving release and refined physical and chemical stability of the formulation. Even with DCM's features and advantages, the excipient functionality can still have an impact on the tablet that is produced with DCM.[25] Excipient-related issues can be resolved by creating new excipients, preparing excipient grades and creating novel combinations of already-existing excipients.[17]

While developing new excipients is an appealing alternate, it is actually a time-consuming and expensive procedure that needs approval from many regulatory agencies for safety and toxicity evaluation. Furthermore, the newly created excipient exhibits a great affinity for heat, moisture and oxidation, which can cause deterioration or cause the excipients' useful features to be lost.[17,26] Furthermore, the excipient functionality may be impacted by the inadequate compressible qualities and fluctuations in the excipient supply.[8] Crospovidone, croscarme, pregelatinized starch, etc. can now be prepared via the creation of new classes of excipients. On the other hand, because of their limited spectrum of potential alterations, the many potential applications of these excipients are limited.[17,27]

In contrast to the first two approaches, the latter-that is, the novel conceivable combination of the existing excipients-was the most practical and appropriate option for resolving the challenges related to the excipient multifunctionality. The blends are mainly classified as physical mixes and co-processed excipients. Physical blends involve the straightforward blending of more than two excipients using the trituration process. Co-processed excipients are made by fusing existing excipients to make new ones.[20,28] This review sought to offer detailed information and a thorough understanding of co-processed excipients, including their fabrication process and their application in different dosage forms.

Co-processed excipients is an intriguing approach mainly used in the food manufacturing to enhance the dispersibility, wettability, gelling properties, solubility and stability of food elements, such as Microcrystalline Cellulose (MCC), MCC and glucomannan,[29] sodium and calcium alginate complex as co-processed excipients.[30] During the 1980s, the pharmaceutical industry began making co-processed materials, leading to the development of the first co-processed excipient made from microcrystalline cellulose and calcium carbonate. Following this accomplishment, several co-processed excipients, such as cellactose (a blend of about 75% cellulose and 25% lactose) with silicified MCC, were developed. The second kind was discovered to be utilized a lot in solid dosage forms.[30]

A co-processed excipient is a particle engineering technique where multiple existing excipients merge at the sub-particle level; entail the incorporation of a particular excipient into the other's particle structure. The technique results in the creation of new excipients with enhanced multifunctional properties, surpassing those of a basic physical blend of the same excipients.[17,19,20,31,32] The generation of co-processed excipients which entails making use of a parent or existent excipients by making some alterations, took place at three stages. Molecular level alterations demonstrate a change in crystalline, amorphous, polymorphism and pseudo-polymorphism features. Conversely, particle level variations occurred in the crystal habit, polytypic arrangement and variations in particle size, shape and distribution was also seen. At the bulk level, the parent excipient reveals a modification in the bulk density, flow characteristics, compressibility and hygroscopicity.[17]

IPEC describes the co-processed excipient as a mixture of two or more compendial or non-compendial excipients that are treated to physically modify their physicochemical assets, which are not feasible to accomplish by plain physical mixing. Due to the engagement of physical mixing, the co-processing procedure retains the chemical identity of both excipients. Usually, co-processed excipients are made by wet granulation, spray drying and co-crystallization methods.[31,33] The working of co-processed excipients remains uncertain; nevertheless, on analyzing available research, it has been found that the tight intermolecular contact between the potential a blend of excipients could be the likely mechanism for the synthesis of co-processed excipients. This approach also offers important numerous advantages including improved performance to that of individual excipient,[34] generally relevant to plastic and brittle materials,[35] and speeding the preparation of commercial formulation devoid of any pricy testing.[36]

Co-processing plastic and brittle materials can lessen the likelihood of capping and lamination following compression by returning the huge quantity of plastic energy.[35] Other advantages shown by co-processed excipients are increase in compressibility and flow characteristics, balancing dilution potential, reducing of lubricant sensitivities and streamlining the tablet production procedures.[37]

Excipient Requirements for the Formation of Co-Processed Excipients

In producing tablets, DCM is the best method when compared to wet and dry granulation. Excipients, however, have an impact on this approach since they particularly alter the tablet's compaction characteristics at large concentrations. Hence, choosing excipients or co-processed excipients with multifaceted qualities is the primary duty of the preformulation scientist.

Transitional repacking, deformity at the site of contact, fragmentation, binding with the clean and fresh surface of particulates, deformation of the solid body, decompression and discharge are some of the processes involved in DCM tablet manufacture. Deformation (compressibility) and bonding (compatibility) are two important powder assets that are most affected during compression and stress.[38] This is because reduction exerts a lot of pressure on the powder blend, which forms the tablet. Conversely, this pressure also causes the particle (i.e., a brittle particle like sucrose, lactose, silicon dioxide, fructose and dextrin) to become internally stressed, which further causes the particle to fragment into small pieces. These tiny pieces show a powerful bond with another particle together with newly surfaced particles. In addition, fragmentation causes the particles to densify, which has allowed smaller particles to enter the gaps left by the larger particles. By altering the particle's shape, the plastic material can exhibit plastic deformation.[39]

Plastic deformation behavior is observed during compression in maize starch, crospovidone, sorbitol, guar gum and polyvinyl pyrrolidone. These kinds of brittle and plastic deformation modifications are necessary to generate fresh and clean surfaces with the higher capacity to develop a fresh bonding. Thus, utilizing this mechanism, it is proposed that the formation of new excipients, i.e., co-processed excipients together with an extra benefit of both an improvement in the mechanism and in multifunctionality of co-processed excipients, could be caused by the contribution of brittle and plastic materials in a proper proportion. Three different combinations of excipients are

normally utilized to make the co-processed excipients: plastic and plastic, brittle and plastic (the most desired combination) and brittle and brittle.[39]

When making co-processed excipients, a blend of excipients that is plastic and brittle is utilised more often than the others. As an illustration, Cellactose co-processed excipients can be considered, which are made of 25% plastic and 75% brittle (lactose). Comparatively speaking, cellactose enhances the binding, flowability, filling and compressibility. Furthermore, the deformation performance of plastic materials is determined by their ideal particle size.[17,40] Employing the same mix of brittle and plastic material, other excipients such as Ludipress, Microcelac, Formaxx, Advantose FS95, Starlac, Xylitab and Pharmatose DCL 40 are also created.

Prosolv, a prime example of a co-processed excipient, is made from a mixture of 98% microcrystalline cellulose (a brittle material) and 2% fumed colloidal silicon dioxide (a plastic material). The two co-processed excipients that are produced by combining brittle and brittle and plastic and plastic excipients are called Dipac and Compressol SM. In the former, the brittle excipients are 97% sucrose and 3% dextrin, while in the later, the plastic excipients are mannitol and sorbitol.[19,27,29] Table 1 lists the enhanced multifunctionality of co-processed excipients-a blend of plastic and brittle materials-that are commercially available.

Technology and Production Methodologies for Co-Processed Excipients

Co-processed excipients may display the multifunctional qualities needed to be advantageous in the tablet-making process. The production and advancement of these multipurpose excipients rely on the choice of brittle or plastic excipients, the right proportion of excipients and the technique for preparing them, as well as the drying process. In comparison with distinct existent excipients, these combined methods can facilitate the development of "engineered," "multifunctional," or "co-processed" excipients with improved flow characteristics, compactibility, compressibility and decreased lubricant sensitivity. From a conceptual standpoint, the procedure of preparing co-processed excipients is incredibly straightforward, requiring only five steps. 1) Excipients are identified and included after a thorough examination of the material's properties; 2) the ideal excipient combination is chosen; 3) the excipients' particle size and solubility are examined, etc. 4) choosing between drying methods including spray and flash drying; and 5) process optimization. On the other hand, the incorrect combination of excipients might result in subpar finished products that show no signs of functionality. As a result, choosing an appropriate procedure and an appropriate experimental design are crucial for producing co-processed excipients (Figure 1).[41,42]

Various techniques that have been documented for the production of co-processed excipients is provided below.

Spray drying method

The method most frequently employed to prepare co-processed excipients is spray drying. The creation of an even dispersion of excipients is the first step in this method. The obtained solution is subsequently atomized to produce excipients in tiny, fine droplets. The droplets are then released into a hot stream of gas, causing spherical particles to form. The spherical excipient particles are

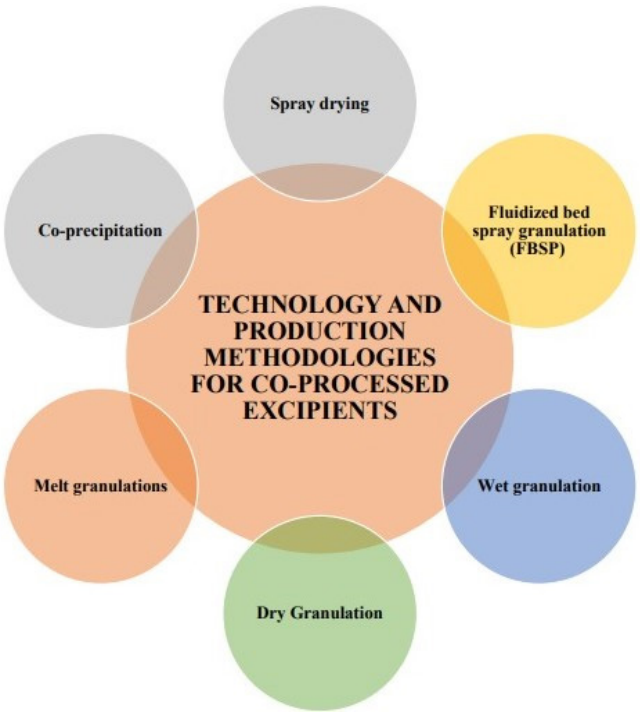

Figure 1: Technology and Production Methodologies for Co-Processed Excipients.

used by the formulation scientist to prepare the tablet because of their better flow and directly compressible nature.

Chauhan *et al*. used spray drying to create co-processed excipients that included lactose monohydrate, MCC and StarCap 500 to enhance the compressible qualities of etodolac. Results indicated that the flow, dilution potential and immediately compressible qualities of etodolac were greatly enhanced by spray-dried based-optimized co-processed excipients with a composition of 25% lactose, 30% MCC and 45% StarCap.[42] To increase HPMC's dispersibility in water, Sharma *et al*. co-processed the material with lactose and sodium chloride using a spray drying technique. The obtained results demonstrate that co-processed HPMC enhanced mechanical characteristics and the aqueous dispersibility time by up to 20 minutes through the interaction of HPMC with lactose and sodium chloride at the sub-particulate or molecular level.[43]

For tableting applications, Wang *et al*. created, enhanced and evaluated co-processed excipients incorporating tri-components such cross-linked Polyvinyl Polypyrrolidone (PVPP)-superdisintegrant, HPMC E3-a binder and α-lactose monohydrate-filler. The disintegration ability of the tablet was found to be greatly improved by the produced tri-component co-processed excipients when they were optimized in a ratio of lactose 200 M, HPMC E3 7% and PVPP 3.5%. These findings were noteworthy as well. The reason for improving the tableting

Table 1: Commercially available co-processed excipients and their enhanced multifunctionality.

Sl. No.	Co-Processed Excipient	Ingredients	Enhanced Multifunctionality
1.	F-Melt C	D-mannitol, microcrystalline cellulose, xylitol, crospovidone, dibasic calcium phosphate anhydrous.	Improved flowability, compressibility and disintegration time.
2.	F-Melt M	D-mannitol, microcrystalline cellulose, xylitol, crospovidone, magnesium aluminometasilicates.	Enhanced properties for tablet formulation.
3.	Pharmaburst	D-mannitol, sorbitol, precipitated silicon dioxide, crospovidone.	Enhanced manufacturability and disintegration time.
4.	Prosolv	D-mannitol, microcrystalline cellulose, fructose, colloidal silicon dioxide, crospovidone.	Facilitates quick dispersion in the oral cavity.
5.	Ludiflash	D-mannitol, crospovidone, polyvinyl acetate.	Improved mechanical properties and resistance to humidity.
6.	MIX	D-mannitol, microcrystalline cellulose, crospovidone, colloidal silica.	Improved properties for direct compression.
7.	Coprocessed Chitin-Calcium Carbonate	Chitin, calcium carbonate.	Improved tabletting performance.
8.	Co-Processed Rice Starch-Based Excipient	Rice starch and other components.	Integrated excipient with the SeDeM-ODT Expert System for direct compression.
9.	Co-Processed Excipients Based on SLN Compritol® 888 ATO/Di-Tab®	SLN Compritol® 888 ATO/Di-Tab® components.	Controlled-release of medication made via direct compression and solid lipid nanoparticles.
10.	Pentaerythritol-Eudragit RS 100	Pentaerythritol, Eudragit RS100.	Enhanced aqueous solubility, *in vitro* dissolution and *ex vivo* permeation of Atorvastatin using solid dispersion carriers.
11.	Compressol® SM	Mannitol, sorbitol blend(s).	Enhanced flow properties and compressibility for tablet manufacturing.
12.	PEARLITOL®	Starch-Mannitol blend(s).	Improved binding properties and tablet hardness in direct compression formulations.
13.	Lactose Monohydrate	Lactose monohydrate compound(s).	Improved tableting performance by fluid-bed melt granulation co-processing.
14.	MicroceLac® 100	Avicel® PH Microcrystalline Cellulose-Lactose blend(s).	Improved compactibility and disintegration properties for tablet formulation.

applications could be due to a higher concentration of HPMC and 30% amorphous lactose.[14]

Fluidized Bed Spray granulation (FBSP)

Another crucial technique for making co-processed excipients is FBSP. In a nutshell, heated air from the granulator's bottom screen is used to prepare the excipient combination before it is fluidized. Simultaneously, the prepared excipient solution is sprayed onto the bottom of the settled powder bed in the opposite direction of the airflow. By combining fine liquid droplets with powder particles, this method produces co-processed granules. To obtain co-processed granules of a consistent size, the resultant granules are subsequently dried and screened. Menon *et al*. demonstrated the use of the FBSP approach to create co-processed excipients with polyvinyl pyrrolidone and corn starch. Co-processed excipients that were fashioned by merging these two excipients demonstrated superior compressibility and free-flowing qualities, which aided in the preparation of immediately compressible tablets.[44]

Wet granulation

The preparation and screening of the wet mass of the powder mixes is a necessary step in the co-processing of excipients by wet granulation. To acquire granules of a consistent size, the resultant granules are subsequently dried and sieved again. To prepare the pill, these granules are compressed and blended.

Using the wet granulation method, Daraghmeh *et al*. produced and characterized a novel co-processed excipient, COP-MC, in the ratio of 2:8 w/w. Following examination, the COP-MC shown strong binding, excellent disintegrability and high compactability as multifunctional qualities for making low strength, high strength and poorly compressible API. Additionally, the outcome implies that the mannitol quantity and granulation method are directly correlated with the COP-MC compaction features.[20] Patel *et al*. synthesized crospovidone and sodium starch glycolate as novel co-processed super disintegrants excipients and tested their effectiveness on cefixime trihydrate and ibuprofen tablets. The innovative co-processed excipients enhanced the tablets' flow and compression characteristics as well as their disintegration and dissolving times.[37]

Dry Granulation

For the fabrication of co-processed excipients, dry granulation uses the roller compactor principle. Excipients that are susceptible to heat and moistness can be used with this technique. This process involves homogeneously blending the powders and compact them using a roller compactor that meets the necessary specifications, including a roller pressure of 5 MPa and a roller speed of 4 rounds per minute. Screws that turn 20 rounds per minute regulate speed. Next, a 710 µm sieve is used to filter the compacted mass that now takes the shape of ribbon material. The resulting uniform-size granules are combined for 10-15 minutes in a 7.5 L cubic blender before being compressed into tablets.[20]

Using a dry granulation approach, Daragemeh *et al*. synthesized the chitin-mannitol as unique co-processed excipients in an optimum ratio of 2:8 w/w to prepare dispersible tablets. The outcomes demonstrated that, in comparison to a traditional tablet, the new co-processed excipient made by combining dry granulation and roller compaction technology offers outstanding multifunctionality, i.e., strong binding, quick disintegration and wetting qualities. The practicality and chemical stability of this co-processed excipient are well preserved by the dry granulation method.[20]

Melt granulations

The following procedures must be followed in order to prepare co-processed excipients using melt granulation techniques: combining and sieving powders, heating, cooling and then sieving again. To put it briefly, the blend of powder to be co-processed is mixed evenly before being sieved to obtain powder particles of a consistent size. After that, the uniform powder is cooked in a porcelain dish container for a reasonable amount of time-roughly 10 to 12 min at a temperature between 50 and 60°C. The mass of the powder breaks down into huge agglomerates when heated. After the agglomerates had cooled to room temperature, they were sieved to produce granules of a consistent size for the tablet's compression.[39]

The melt granulation technique was used by Garg *et al*. to create co-processed excipients based on PEG 4000 and crospovidone. The flowability and compressibility of the native excipients were enhanced by Box-Behnken design-based co-processed excipients in an ideal balance of crospovidone (7.5% w/w), PEG 4000 (15% w/w) and heating duration (12 min). Additionally, when compared to traditional wet granulation tablets, the optimized co-processed excipients significantly improved tablet properties like hardness and disintegration time *in vitro* drug release.[39]

Sherman *et al*. solved the abrasiveness and capping issue they faced during tablet formulation by co-processing calcium phosphate with glyceryl palmitostearate or behenate using the melt granulation method. Excipients co-processed with this innovation produced unique tableting effects in venlafaxine besylate prolonged release tablet and venlafaxine HCl extended release tablet.[45]

Co-precipitation

Aqueous solutions of the different excipients to be co-processed must be prepared and mixed in order to prepare co-processed excipients, employing the co-precipitation method. Co-precipitates, or suspended particles, are formed when excipients react with one another, as demonstrated by the mixing of excipient solutions. To get a consistent particle size, this product is subsequently strained, oven-dried and sifted.

These particles are compacted into a tablet after being utilized as co-processed excipients to make granules. Co-precipitation can also be achieved by a number of techniques, such as freeze and spray drying, pH changes, wet and dry granulation and freezing.

Chitin Metal Silicates (CMS) were prepared as co-processed excipients by Hamid *et al.* using the co-precipitation method. The findings demonstrated that, in comparison to wet granulation, CMS considerably functions as a filler, binder and super disintegrating agent for tablets made by direct compression. In particular, tablets based on CMS exhibited a superior dissolving and disintegration profile. CMS is also compatible with neutral, essential and acidic medications, making it a flexible co-processed excipient for production of controlled and sustained-release tablets.[46]

Utilizing the co-precipitation approach, Badwan *et al.* formed co-processed excipients by means of colloidal silica and starch. This approach has produced co-processed excipients that have shown significant multi-functionality as disintegrants and fillers and as a result, they may find successful application in immediate-release dosage forms.[47]

Safety and Risk Concerns of Co-Processed Excipients

The usage of excipients in pharmaceutical formulations needs to be based on their priority. There are two approaches used for the assessment of the safety and risk excipients: 1) when the excipients have a history of utilization and 2) when the excipient has no history of utilization.[48] The first asserts that these excipients have undergone safety testing and are effectively utilized as food additives in prescription formulations. Furthermore, the official pharmacopeias already contain safe excipients. Since the second set of excipients are however unsafe, it hasn't been previously utilized in any formulations.[49]

Regulatory bodies such as the USFDA, which has "Nonclinical Studies for the Development of Pharmaceutical Excipients," USP-NF 26, which has "Excipients Biological Safety Evaluation Guidelines," and IPEC, which has regulations on "New Excipients Evaluation Guidelines" and "Proposed Guidelines for Safety Evaluation of New Excipients," have recommended the guidelines that are required for the incorporation of such excipients in pharmaceutical formulations. Support for these recommendations aids in evaluating the safety of novel pharmaceutical excipients. Similarly, it is the main obligation of producers of novel excipients to ask regulatory bodies to integrate safety data into guidelines for new excipients.[10]

Quantitative Structure-Activity Relationships (QSARs) can be used to evaluate the risk associated with co-processed excipients. QSAR is a sophisticated analytical method that is successfully used to assess whether a chemical modification has occurred or not and to look for the emergence of new contaminants in the co-processed excipients. The shorter studies can examine the safety of co-processed excipients in place of toxicological assessments. Additive behavior needs to be carefully assessed in co-processed excipients since a mixture of two or more excipients might be susceptible to potential interaction. Co-processed excipients are one kind of novel excipient, just like New Chemical Entities (NCE). It also needs extensive details on its chemical nature, manufacturing process, control data and toxicological evaluation.[10]

Under section P4.6, the generated and gathered evaluation data on new or novel excipients needs to be kept in a specific design document, called a Common Technical Document (CTD). Toxicological information on the new excipients can also be added to the Drug Master File (DMF) type IV or V. The IPEC has also created the specific Excipient Master File to include any supporting data for excipients that need to be submitted to different regulatory bodies. The safety and assessment of recently created co-processed excipients must be conducted using the IPEC-designed New Procedure for Excipients (NPE). Reducing the risk associated with the use of novel excipients in pharmaceutical formulations is the principal objective of this process.[50]

Applications of Co-Processed Excipients

Co-processed excipients can exhibit multifunctional qualities without exhibiting any obvious signs of a chemical alteration in the integrated or preexisting excipients. This means that this adaptable excipient may find use in the development of biological, semisolid, parenteral and liquid formulations, in addition to solid oral formulations. The various applications of co-processed excipients in these formulations are discussed below (Figure 2).

Solid oral dosage forms

The production of tablets and excipients are important factors in the development of solid oral dosage forms. Nevertheless, the formulation of tablets using directly compressible approach may likely be hampered by the intrinsic problems with native excipients, like their flow and direct compressible qualities. Recent investigations in literature have revealed that lactose or cellulose have been used in the development of the majority of co-processed excipients.[51] Using a mixture design, Apeji *et al.* have produced and fine-tuned starch-based co-processed excipients for tablets intended for direct compression. Compared to native starch, starch-based co-processed excipients with the ideal proportions of tapioca starch (90%) and gelatine (7.5%) and colloidal silicon dioxide (2.5%) demonstrated notable multifunctionality in terms of compatibility, Hausner's ratio, angle of repose and compressibility. When compared to Prosolv® and StarLac, directly compressible tablets made with these co-processed excipients significantly enhanced the drug release and disintegration time while meeting USP specifications.[27]

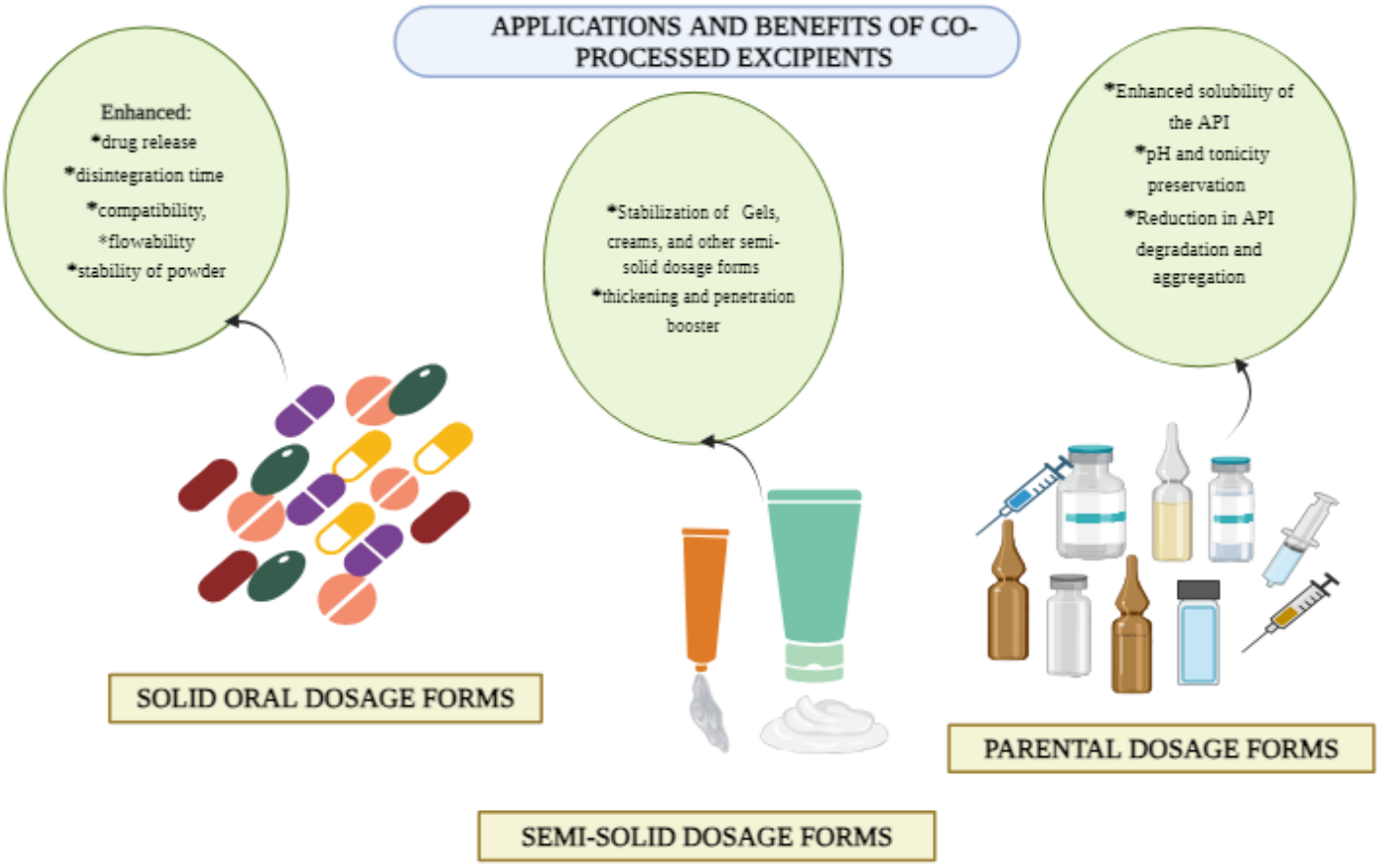

Figure 2: Applications and Benefits of Co-Processed Excipients.

The co-processed excipients comprising starch, MCC and chitin were produced by Assaf *et al*. using hydrophilic polymers on magnesium silicate. Studies on characterization have demonstrated that the effective incorporation of magnesium silicate into hydrophilic polymers enhanced the compatibility, flowability and stability of powder. Moreover, it improved the tablet's crushing strength, disintegration speed and added quick drug dissolution.[22]

Semi-solid dosage forms

Semi-solid dose forms make up the majority of pharmacological content. Unfortunately, some solid excipients exhibit subpar physicochemical properties which compromises the final products' quality. In order to improve the transdermal route bioavailability, feel, appearance and efficacious delivery, additional excipients have been developed. One effective excipient for creating semi-solid forms is gelucire. It is often created by an interaction between fatty acids and Polyethylene Glycol (PEG), where the latter is lipophilic and the former is hydrophilic. Surfactants are created when PEG and fatty acids with different molecular weights combine to provide an extensive variety of Hydrophilic-Lipophilic Balance (HLB) values.[52-54]

Because of its unique characteristics, gelucire may be used as a co-processed excipient in semi-solid preparations. Gels, creams and other semi-solid dosage forms are stabilized in these dosage forms by gelucire. It also serves as the transdermal delivery system's thickening and penetration booster. The in-situ emulgel containing piroxicam was made by Saxena *et al*. using low-viscosity grades of sodium alginate and varying amounts of melted gelucire 39/01. They assessed how it affected the response that inhibits inflammation. When compared to traditional in situ gel, the generated in situ emulgel showed a notable improvement in the analgesic/anti-inflammatory activity.[55] Semisolid lipid Matrix (SSM) formulation was created and analyzed by Kalpana *et al*. with different gelucire mixes (44/14, 50/13/, 33/01 and 43/01), PEG (4000 and 6000) and poloxamer 188. It was discovered that the SSM formulations with gelucire (44/14, 50/13/, 33/01 and 43/01) significantly improved the sustained solubility of aceclofenac for up to 24 hr.[56]

Parental dosage forms

In order to aid maintain stability all through their production to storage, parenteral formulations must contain an exact, precise type and number of excipients and/or co-processed excipients. The expanding field of formulations is biological and parentral formulations. However, physico-chemical degradation could be

caused by its intrinsic instability. Excipients and co-processed excipients could be used appropriately to address this stability issue. Suitable excipients are added to biological products and serve a variety of purposes, including enhancing the solubility of the API, extending its shelf life, preserving the formulations' pH and tonicity during use, preserving the stable proof of the protein and vaccine and reducing API degradation and aggregation. Additionally, excipients can be used as bulking agents, antioxidants, or preservatives.[57] Adjuvant excipients are employed in vaccination formulations instead of biological ones and they have the power to either demonstrate or improve the therapeutic action of API or boost the added antigen's capacity to activate the human immune system.

Regulatory Considerations for Co-Processed Excipients

Every novel excipient must be approved by a number of regulatory bodies for both safety and effectiveness. The regulatory bodies' approvals validate the excipient's entry into the pharmaceutical market. The process of getting a drug product approved by the USFDA begins with the submission of an NDA (New Drug Application) or an ANDA (Abbreviated New Drug Application), along with comprehensive details about the Active Pharmaceutical Ingredient (API), different components and related excipients. The composition statement, safety data sheet, specification and application of any advanced analytical approach for the evaluation of the API and excipients must all be included in the extensive report. According to federal laws, excipients' safety information (Drug and Cosmetic Act, 1938) is typically used to determine how they should be used in planned formulations.

Excipients must have their pharmacological evaluations done in accordance with International Conference on Harmonization (ICH) rules in addition to their toxicological assessments. Excipients are important compounds or groups that give the finished formulations strong integrity, as was previously mentioned. It can, however, be scientifically altered in accordance with the recommendations for mixing excipients and taking into account their anticipated application in pharmaceutical formulations. Single excipients with improved multifunctional qualities are formed through the alterations of the current excipients, i.e., co-processed excipients, involving two or more existent excipients at the sub-particle level.

Furthermore, it has been claimed that the co-processing only displays the physical alterations of the integrated excipients and does not result in any chemical modifications. With one requirement: the parent combined excipients must also have the same nature in order for the co-processed excipients to be safe under the GRAS category. Therefore, in order to approve co-processed excipients, this prerequisite eliminates the need for further toxicological and pharmacological research. Despite the co-processed excipients' highest level of safety, producers have nonetheless had a significant issue when it came to adding them to the official monograph. The pharmaceutical excipients business was unable to smooth its introduction into the market due to this substantial obstacle. Furthermore, only a handful of co-processed excipients, including compressible sugar, spray-crystallized dextrose-maltose and dispersible cellulose, have official status with the USP-NF and British Pharmacopoeia. Likewise, the third edition of the handbook of pharmaceutical excipients includes the recently produced Avicel CE15 and Silicified Microcrystalline Cellulose (SMCC) co-processed excipients.

CONCLUSION

According the literature findings, pharmaceutical excipients are necessary for contemporary dosage formulations. The first weighing, middle and packing procedures all have inferior problems when it comes to native excipients. This issue can be somewhat remedied via the implementation of cGMP methods by the pharmaceutical sector. To solve the problems with the native excipients, it is therefore imperative to employ the alternative strategy. To enable formulation scientists, grasp the advantage and value of co-processed excipients in producing different pharmaceutical dosage forms, the most relevant, adequate and feasible solution is a multifunctional co-processed excipient.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IPEC: International Pharmaceutical Excipients Council; **USFDA:** United States Food and Drug Administration; **USP:** United States Pharmacopoeia; **API:** Active Pharmaceutical Ingredients; **BSC:** Biopharmaceutical Classification System; **IIG:** Inactive Ingredients; **GRAS:** Generally Regarded as Safe; **DCM:** Direct Compression Technique; **MCC:** Microcrystalline Cellulose; **HPMC:** Hydroxypropylmethylcellulose; **PVPP-** Polyvinylpolypyrrolidone; **FBSP:** Fluidized Bed Spray; **COP-MC:** Co-Processed Microcrystalline Cellulose; **CMS:** Chitin Metal Silicates; **USFDA:** United States Food and Drug Administration; **USP-NF:** United States Pharmacopeia-National Formulary; **QSARs:** Quantitative Structure-Activity Relationships; **NCE:** New Chemical Entities; **CTD:** Common Technical Document; **DMF:** Drug Master File; **NPE:** New Procedure for Excipients; **USP:** United States Pharmacopeia; **PEG:** Polyethylene Glycol; **HLB:** Hydrophilic-Lipophilic Balance; **SSM:** Semisolid Lipid Matrix; **NDA:** New Drug Application; **ANDA:** Abbreviated New Drug Application; **ICH:** International Conference on Harmonization; **SMCC:** Silicified Microcrystalline Cellulose.

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