REVIEW ARTICLE

Coprocessed Excipients: Multifunctional Excipients for Solid Oral, Liquid, Semisolid, Parenteral, and Biological Preparations

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Abstract

In pharmaceutical dosage forms, the excipient represents a unique and significant substance with equal importance to active pharmaceutical ingredients (API) because it offers numerous benefits to the final formulations. Benefits include filling the tablet's total volume, enhancing API absorption and bioavailability, and increasing organoleptic properties. However, the diverse nature of excipients, API-excipients incompatibility, moisture absorbing ability, surface acidity of the excipients, crystal nature, and generation of inferior toxic excipients, etc., may create a big problem in selecting appropriate excipients. The excipients high toxicity may substantially impact the formulation and API's pharmacokinetic and pharmacodynamic nature. It may likely be due to using multiple excipients with incompatible performance. Adopting and implementing cGMP in the pharmaceutical industry can solve the issues related to excipients; however, it still affects the excipients manufacturing process in terms of its time-consuming, high cost, and lengthy approval process. With their multifunctional properties, coprocessed excipients can provide special offers to formulation scientists when manufacturing dosage forms. The need for coprocessed excipients, requirements of excipients to be coprocessed, manufacturing technology, risk and assessment studies, application, and regulatory compliance provide an alternate and promising approach for selecting and using an appropriate combination of existing excipients over the native excipients in the formulation of dosage forms.

Key words: Coprocessed excipients, manufacturing technologies, pharmaceutical excipients, regulatory requirements

INTRODUCTION

Pharmaceutical excipients are substances or groups employed in a broad range as vehicles or carriersto provide volume, uniformity, and consistency to the various dosage forms. These valuable properties of excipients are exhibited from their initial weighing to the manufacturing process and from manufacturing to the patient administration process.[1,2] According to the United States Food and Drug Administration (USFDA), the United States of Pharmacopoeia (USP), and the International Pharmaceutical Excipients Council (IPEC) also defines excipients as non-pharmacological substance which is present in large quantity in final formulation other than active pharmaceutical ingredients (API). The inert nature of excipients demonstrates their several usefulness.[3] The excipients are used as diluents, fillers, coloring, flavouring, and preserving agents in traditional dosage forms such as conventional tablets and capsules, creams, ointments, and pastes. Recently, it has been observed that the excipients in an advanced dosage also play a significant role as solubility and absorption enhancers,[4,5] emulsifying agents,[6] wetting agents,[7] and release modifiers[8,9] for enhancing or improving the poor solubility, permeability, and bioavailability of biopharmaceutical Classification System class drugs. Due to

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inert and beneficial advantages, pharmaceutical excipients are accepted as unique and significant substances with the same importance as the API of the final formulations.[10] In most dosage forms, the excipients are added more (i.e., 1–99%) than API. The added excipients as per the above range with API provide a broad range of functions to the final formulations, such as filling the total volume/weight of final dosage forms, controlling the stability of API by lowering its degradation, enhancing the accuracy of API dose in the final formulation, enhance absorption and bioavailability of API, increases the organoleptic characteristics such as colour, odour and taste, and finally, patient compliance and acceptance. Excipients also increases the elegance of the final formulation; thus, it is suitable for patient administration via different routes. Apart from these, the excipients safety and effectiveness are another prime importance and correlate well with the multiple functions of excipients.[11-13] Various sources of excipients such as animal, mineral, biotechnological, and chemical reactions determine its safety, effectiveness, and, most importantly, compatibility with the API in dosage forms. Recently, a significant development in pharmaceutical technology has demonstrated the simple and effective way of assessing the safety, effectiveness, and mixing behavior of excipients to excipients and excipients to API.[14] Therefore, the excipients, their preparation, and their selection with API impact the patient's final preparation and acceptance.

In formulation development, selecting excipients is essential because excipients with good physicochemical properties have shown better compatibility with the API. The excipient-API compatibility gives final clearance to the formulation scientist for manufacturing predetermined dosage forms.[15] However, selecting suitable excipients for the API is not simple due to the diverse nature of excipients such as solid, liquid, semisolid, and gaseous. These excipients are also investigated for their physicochemical properties such as moisture absorbing ability, acid-base interaction studies, surface acidity of the excipient, and formation of defects on the surface of excipients, crystal nature, and presence of any oxidative reactants products. Moreover, while manufacturing, there is a possible chance of the generation of inferior products with a high level of toxicity. The toxicity within the excipients may be due to using multiple excipients and incompatible behavior between selected excipients and API. Excipient toxicity indicates its loss of inert nature and, thereby, reacts with API and forms undesirable toxic products.

Moreover, the toxic excipients have likely modified the pharmacokinetic as well as pharmacodynamic behavior of the API in the formulation.[16] The toxicity issues related to the excipients have been solved by adopting and implementing the same good manufacturing practices (cGMP) already implemented for API. However, this approach may influence the formulation scientist during excipient manufacturing, such as time-consuming, increasing cost, and, most importantly, approval from various regulatory agencies. Excipient manufacturing is not a single-step process but takes multiple steps, such as harvesting, extraction, chemical synthesis, accumulation, particle size reduction, and fermentation. With the combination of these various steps, the new excipient is often manufactured as a continuous or batch process. The developed new excipient comes with a high cost and an extensive regulatory review process, the same as API. The review process is specially carried out to assess excipient safety, quality, effectiveness, and functionality.[17] USFDA has maintained the obtained results for each new and existing excipient in their database named "inactive ingredients (IIG)." Additionally, the authorized excipient is accepted as "GRAS," or "Generally Regarded As Safe." The manufacturer might use the IIG database as a platform to choosing the needed and API-compatible excipients to create appropriate dosage forms. The involvement of multiple steps increases the excipients development cost, further influencing its selection and utilization in the formulation.

A successful pharmaceutical dosage form without an excipient is impossible because formulation functionality is often likely dependent on the pharmaceutical excipients apart from API.[18,19] It has also been observed that adding a single excipient or two excipients in a simple physical mixture cannot produce a multifunctional excipient specifically needed for solid dosage forms.[20] Among all dosage forms, the concrete oral dosage forms, i.e., granules, pellet, tablet, and capsules, have occupied more than 70% of the total population of pharmaceutical preparation and still it has been considered one of the preferable dosage forms because it offers multiple benefits to formulator as well as to the patients. This benefit includes simple and economical preparation methods, ease and suitability of administration, simple packing, shipping, and dispensing process, accuracy in dose administration, compactness, and high stability. Multiple benefits of tablets specifically depend on the excipients.[21] Nearly 70–80% of pharmaceutical dosage forms contain higher numbers and concentrations of pharmaceutical excipients.[22] Higher concentration of excipients likely affects the functional properties and processability/method of preparation of tablets.[23] Compared to wet and dry granulation, the direct compression method (DCM) is the most efficient method for the preparation of the tablet due to the involvement of only preparation and then compression of a dry mixture of API and excipient using a tablet compression machine. Besides this, DCM exhibits multiple benefits, which include one to two processing steps, improved variable dissolution release, improved physical and chemical stability of the formulation, and lowering bacterial contamination.[24] Despite DCM advantages and benefits, the tablet prepared by DCM is still affected by excipients functional properties.[25] Problems related to excipients can be solved by developing new excipients, preparation of new grades of excipients, and fresh combinations of existing excipients.[17]

New excipient development is a good alternative, but in actual sense, it is a time- and money-consuming process that requires safety and toxicity evaluation permission

from various regulatory agencies. Moreover, the recently developed new excipient shows a strong affinity toward moisture, heat, and oxidation, resulting in damage or loss of excipients' functional properties excipients.[17,26] In addition, the deficient compressible properties and variation in excipients supply could likely be the reasons for affecting the excipients functionality.[8] Making new grades of excipients is now a viable way to make pregelatinized starch, croscarme, crospovidone, and other similar products. Conversely, the multiple uses of these excipients are restricted due to their narrow range of possible modifications.[17,27]

Compared to the previous two methods, the latter, i.e., the new possible combination of the existing, was the most suitable and convenient technique for overcoming the excipient multifunctionality issues. These combinations are majorly categorized into physical mixtures and coprocessed excipients. In physical mixtures, there is a simple physical mixing of two or more excipients prepared by the trituration method. In contrast, coprocessed excipients are developed by forming new excipients via a combination of existing excipients.[20,28] This review aimed to provide insights and comprehensive knowledge regarding coprocessed excipients, their manufacturing, and their use in various dosage forms.

A coprocessed excipient is a novel technique primarily introduced in the food industry for improvement in solubility, wettability, dispersibility, stability, and gelling properties of food ingredients, for example, microcrystalline cellulose (MCC) and glucomannan,[29] MCC, sodium, and calcium alginate complex[30] as coprocessed excipients. In the 1980s, the pharmaceutical industry entered the coprocessed manufacturing field, followed by the preparation of the first coprocessed excipients composed of MCC and calcium carbonate. With this success, additional coprocessed excipients, i.e., Cellactose (approximate combination of 75% cellulose and 25% lactose) and silicified MCC were formulated. From these two, the latter one was found to be used more frequently in the solid dosage forms.[30]

When more than two excipients are combined at the sub particle level in particle engineering, the process is known as coprocessing. This allows one excipient to be incorporated into the particle structure of another excipient, further resulting in the formation of new excipients (single components) with improved and superior multifunctional characteristics when compared to a simple physical mixture of the same combination of excipients.[17,19,20,31,32] The formation of coprocess excipients engages the engineering of a parent or existing excipients via changes to place at three levels. Molecular level changes show the alteration in crystalline, amorphous, polymorphism, and pseudo-polymorphism properties. In contrast, particle level changes occur in crystal habit, polytypic arrangement, and changes in particle size, shape, and distribution. At the bulk level, the parent excipient displays the alteration in the bulk density, flow properties, compressibility, and hygroscopicity.[17] IPEC defines the coprocessed excipient as a combination of two or more compendial or non-compendial excipients that are processed to physically alter their physicochemical properties, which are not possible to attain using the simple physical mixture. Due to the involvement of physical mixing, the coprocessing technique maintains the chemical integrity of both excipients. Usually, coprocessed excipients are manufactured by spray drying, wet granulation, and cocrystallization method.[31,33] The mechanism for coprocessed excipients is still unclear; however, on reviewing the literature, it has been observed that the close intermolecular interaction between the possible combinations of excipients could be the possible mechanism for the formation of coprocessed excipients. Moreover, this technology offers significant multiple benefits like enhanced functionality to that of individual excipients,[34] broadly applicable to plastic and brittle materials,[35] and accelerating the preparation of commercial formulation without any expensive testing.[36] Coprocessing plastic and brittle materials helps reduce the risk of capping and lamination during compression by restoring the large amount of plastic energy.[35] Additional benefits demonstrate by coprocessed excipients are improvement in compressibility and flow properties, balancing dilution potential, lowering of lubricant sensitivity, and simplifying the tablet production process.[37]

REQUIREMENT OF EXCIPIENTS FOR FORMATION OF COPROCESSED EXCIPIENTS

DCM is the most suitable approach for the production of tablets compared to wet and dry granulation. However, this method is affected by excipients because, at high concentrations, it specifically modifies the compaction properties of the tablet. Therefore, it is the prime responsibility of the preformulation scientist to select excipients or coprocessed excipients which show multifunctional properties.

Tablet manufacturing by DCM involves several events, i.e., transitional repacking, deformation at the point of contact, fragmentation, bonding with the new and clean surface of particles, deformation of the solid body, decompression, and ejection. Among these, the powder's deformation (compressibility) and bonding (compatibility) are important characteristics that are most often affected during compression and stress[38] because reduction exerts a lot of pressure on the powder blend, which forms the tablet, while also creating internal stress in the particle (i.e., brittle particles like sucrose, lactose, silicon dioxide, fructose, and dextrin), which further causes fragmentation to produce small fragments These smaller fragments, accompanied by new and clean surfaces, exhibit strong bonding with another particle. Besides this, fragmentation has also done the densification of particles resulting in the penetration of smaller particles into the void spaces between the large particles. The plastic material can demonstrate plastic deformation by changing the shape of

the particles. Polyvinylpyrrolidone, crospovidone, maize starch, guar gum, and sorbitol show plastic deformation behavior during compression. These types of brittle and plastic deformation changes are required to form new and clean surfaces with the increased potential to establish new bonding. Therefore, based on this mechanism, it is suggested that the contribution of brittle and plastic materials in an appropriate ratio could be responsible for forming new excipients, i.e., coprocessed excipients with the added advantage of both the mechanism as well as improvement in the multifunctionality of coprocessed excipients. Typically, the coprocessed excipients are manufactured using three possible combinations of excipients, i.e., brittle and plastic excipients (most preferred one), plastic and plastic, and, the last one, brittle and brittle.[39] The plastic and brittle combination of excipients is the majorly used combination for preparing coprocessed excipients compared to rest. For example, the Cellactose, coprocessed excipients manufactured using 75% brittle (i.e., lactose) and 25% plastic (i.e., cellulose). Cellactose improves the filler, binding, flow ability, and compressibility compared to others. Moreover, the optimum particle size of plastic materials determines its deformation performance.[17,40] Other excipients, Ludipress, Pharmatose DCL 40, Starlac, Xylitab, Advantose FS95, Formaxx, and Microcelac, are some examples that are also prepared using the same combination of brittle and plastic material. One example of coprocessed excipients, i.e., Prosolv, has been prepared using a combination of 2% fumed colloidal silicon dioxide (as plastic material) and 98% MCC (as brittle material). Dipac and Compressol S are the two coprocessed excipients manufactured using a combination of brittle and brittle and plastic and plastic excipients. The first one comprises 97% sucrose and 3% dextrin as brittle excipients, whereas the latter consists of mannitol and sorbitol as plastic excipients.[19,27,29] Table 1 describes marketed coprocessed excipients, a combination of brittle and plastic materials, and their improved multifunctionality.

MANUFACTURING AND TECHNOLOGIES USED TO PREPARE COPROCESSED EXCIPIENTS

Coprocessed excipients can exhibit multifunctional characteristics that are required to be helpful for the manufacturing of tablets. The manufacturing and development of these multifunctional excipients depend on selecting either plastic or brittle excipients, the appropriate ratio of excipients chosen, and the preparation and drying process method. These combined processes together can promote the preparation of "engineered," "multifunctional," or "coprocessed" excipients with improved flow properties, compressibility, compactibility, and reduced lubricant sensitivity compared to individual existing excipients.

From the concept point of view, the preparation of coprocessed excipients is very easy and simple because it involves only five steps: (1) Identification of excipients that are incorporated based on careful study of material characteristics, (2) selection of the desired combination of excipients, (3) analysis of excipients particle size and solubility, (4) selection of drying processes such as spray drying and flash drying, and (5) process optimization. However, the wrong combination of excipients can form inferior products without any sign of functionality. Therefore, it is essential to identify a suitable process and a proper experimental method for preparing coprocessed excipients.[41,42] Since 1988 to till now, various methods have been reported so far for the manufacturing of coprocessed excipients and all of them are briefly discussed below.[39]

Spray drying

Spray drying is the widely used technique for the preparation of coprocessed excipients. This process is started with the preparation of homogenous dispersion of excipients. The prepared solution is then atomized to get small fine droplets of excipients. These droplets are then passed into a moving stream of hot gas, resulting in spherical particles forming. The formulation scientist uses excipients spherical particles to prepare the tablet due to improved flow and directly compressible properties. Chauhan *et al*. have developed coprocessed excipients for improving the compressible properties of etodolac using MCC, lactose monohydrate, and StarCap 500 via the spray drying method. The flow, dilution potential, and immediately compressible qualities of etodolac were greatly improved by spray-dried based-optimized coprocessed excipients (having the composition of 30% MCC, 25% lactose, and 45% StarCap).[42] Sharma *et al*. performed the coprocessing of HPMC with lactose and sodium chloride using a spray drying method to improve its dispersibility in water. The obtained results have shown that coprocessed HPMC improved the aqueous dispersibility time up to 20 min and mechanical properties via the involvement of subparticulate or molecular level-based interaction of HPMC with lactose and sodium chloride.[43] Wang *et al*. developed, optimized, and characterized coprocessed excipients containing tricomponents such as α-lactose monohydrate (a filler), HPMC E3 (a binder), and cross-linked polyvinylpolypyrrolidone (PVPP) (superdisintegrants) for tableting applications. The study results showed that developed tricomponent coprocessed excipients in an optimized ratio of lactose 200 M, HPMC E3 7%, and PVPP 3.5% significantly improved the compatibility and, most importantly, the disintegration ability of the tablet. Higher HPMC concentration and 30% amorphous lactose could be the reason for enhancing the tableting applications.[44]

Fluidized bed spray granulation (FBSP)

FBSP is another important method used for the preparation of coprocessed excipients. Briefly, the mixture of the excipients is prepared and then subjected to fluidization in the presence of hot air from the granulator's bottom screen.

At the same time, the prepared excipient solution is sprayed in the opposite direction of the airflow on the bottom of the settled powder bed. This mechanism leads to the formation of coprocessed granules by mixing fine liquid droplets with the powder particles. The resulting granules are then dried and screened to get uniform-size coprocessed granules. Menon *et al*. showed the utilization of the FBSP method to formulate coprocessed excipients containing corn starch and polyvinylpyrrolidone. Formulated coprocessed excipients using a combination of these two excipients showed an excellent free-flowing and better compressible characteristic to help prepare directly compressible tablet.[45]

Wet granulation

Coprocessing of excipients by wet granulation involves the preparation and sieving of the wet mass of the powder mixtures. The obtained granules are then subjected to drying and, further, sieved to get a uniform size of the dry granules. These granules are remixed and compressed for the preparation of the tablet. Daraghmeh *et al*. prepared and characterized a novel coprocessed excipients, i.e., COP-MC, in the ratio of 2:8 w/w using the wet granulation method. After evaluation, the COP-MC showed significant binding, highly compactable, and superdisintegrable as multifunctional properties for preparing poorly compressible, high strength, and low strength API. Moreover, the result also suggests that COP-MC compaction properties are directly proportional to the quantity of mannitol and granulation technique.[20] Gohel *et al.* prepared the novel coprocessed superdisintegrants excipients to consist of crospovidone and sodium starch glycolate and evaluated its efficacy on cefixime trihydrate and ibuprofen tablets. Novel coprocessed excipients not only improved the flow and compression properties but also improved the disintegration and dissolution time of both tablets.[24]

Dry granulation

Dry granulation adopts the principle of roller compactor for the preparation of coprocessed excipients. This method is suitable for moisture and heat-sensitive excipients. In this method, the powders are blended uniformly and then compacted using a suitable roller compactor with optimized conditions such as 5 MPa roller pressure and four rounds/minute roller speed. Screw speed control is 20 rotations per minute. The compacted mass in the form of ribbon material is then sieved using a 710 μm sieve. The obtained uniform-size granules are mixed in a 7.5 L cubic blender for 5 to 10 minutes and, finally, used these granules for compression into tablets. Daraghmeh *et al*. prepared the chitin-mannitol as novel coprocessed excipients in an optimized ratio of 2:8 w/w using a dry granulation method to prepare dispersible tablets. Results showed that novel coprocessed excipient prepared by combined dry granulation and roller compaction technology provides excellent multifunctionality, i.e., strong binding, rapid disintegration, and wetting properties to the prepared orodispersible tablet compared to a conventional tablet. The dry granulation method well preserves this coprocessed excipient's functionality and chemical stability.

Melt granulations

Preparation of coprocessed excipients using melt granulation techniques involves the following steps: mixing and sieving powders, heating, cooling, and, finally, sieving. In brief, the powder mixture to be coprocessed is blended uniformly and then sieved to get a uniform size of the powder particles. The homogenous powder is then heated at a suitable temperature range of 50–60°C in a porcelain dish container for a sufficient period, i.e., 10–12 min. Heating leads to the breakdown of powder mass into large agglomerates. The agglomerates cooled to room temperature and then sieved to obtain a uniform size of the granules for the compression of the tablet. Garg *et al*. have adopted the melt granulation method to prepare crospovidone and polyethylene glycol (PEG) 4000-based coprocessed excipients. Box-Behnken design-based coprocessed excipients in an optimized ratio of crospovidone (7.5% w/w), PEG 4000 (15% w/w), and heating time (12 min) improved the flowability and compressibility of the native excipients. Furthermore, the optimized coprocessed excipients appreciably improved tablet characteristics such as hardness and disintegration time *in vitro* drug release compared to conventional wet granulation tablet.[39] Escoi *et al.* utilized the melt granulation method to coprocess calcium phosphate with glyceryl palmitostearate or behenate to overcome the abrasiveness and capping problem encountered when formulating the tablet. Coprocessed excipients with this improvement gave special tableting effects in venlafaxine HCl modified release tablet and venlafaxine besylate extended release tablet.[46]

Coprecipitation

Preparation of coprocessed excipients using the coprecipitation method involves the preparation and mixing of aqueous solutions of various excipients that are to be coprocessed. Mixing of excipients solutions may show the reaction between excipients, which further results in the formation of suspended particles, i.e., coprecipitates. This product is then filtered out, dried in an oven, and sieved to get uniform particle size. These particles are used as coprocessed excipients to prepare granules and then compressed into a tablet. Various methods also perform coprecipitation's includes wet and dry granulation, change in pH, freeze and spray drying. Hamid *et al*. utilized the coprecipitation method to prepare chitin metal silicates (CMS) as coprocessed excipients. Results showed that CMS significantly acts as a filler, binder, and superdisintegrating agent for tablets prepared by direct compression compared to wet granulation. CMS-based tablets especially showed a better disintegration and dissolution profile. Moreover, CMS offers compatibility

with acidic, essential, and neutral drugs, and therefore it can be used as versatile coprocessed excipients for the manufacturing of controlled and sustained release tablet.[47] El-Barghouthi *et al*. prepared coprocessed excipients using starch and colloidal silica via the coprecipitation method. Obtained coprocessed excipients utilizing this method have demonstrated considerable multifunctionalities such as filler and disintegrants and, therefore, could be used successfully in immediate-release dosage forms.[48]

SAFETY AND RISK ASSESSMENT OF COPROCESSED EXCIPIENTS

In pharmaceutical formulations, the use of excipients must depend on their precedence. The safety and risk assessment of excipients is carried out in two ways: (1) The excipients have precedence of use and (2) the excipient has no precedence of use.[49] The first indicates that safety tests were carried out on these excipients and have been used successfully as a food additive in pharmaceutical formulations. Moreover, safe excipients have already been included in the official pharmacopeia. The latter excipient is those that are not safe; hence, it has never been used in any formulations.[50] The use of these excipients in pharmaceutical formulations necessitates following the guidelines recommended by regulatory bodies like the USP-NF 26 "Excipients Biological Safety Evaluation Guidelines," the USFDA "Nonclinical Studies for the Development of Pharmaceutical Excipients," and IPEC "New Excipients Evaluation Guidelines" and "Proposed Guidelines for Safety Evaluation of New Excipients". The support of these guidelines helps assess new pharmaceutical excipients' safety. Similarly, it is also the primary responsibility of new excipients manufacturers to request the regulatory agencies to include the safety information in the guidelines for future excipients.[10]

The risk assessment of coprocessed excipients can be carried out by Quantitative Structure–Activity Relationships (QSARs). QSAR is an advanced analytical technique employed effectively to evaluate the presence or absence of any chemical change and to check the formation of any new impurities in the coprocessed excipients. Instead of toxicological studies, the abbreviated studies can evaluate the safety assessment of coprocessed excipients. In coprocessed excipients, a combination of two or more excipients may be liable for possible interaction; therefore, the additivity should be evaluated carefully. As with new chemical entities, coprocessed excipients are one type of new excipients. It also requires detailed data about toxicology evaluation, its chemistry, manufacturing procedure, and control information. The generated and collected assessment information on new or novel excipients must be stored in a particular design document, i.e., a common technical document under section P4.6. In addition, the Drug master file type IV or V is also available to add toxicological data on the new excipients. Similarly, the IPEC has also developed the particular Excipient Master File to add any excipients supporting information for submission to the various regulatory agencies. The New Procedure for Excipients designed by IPEC has to be used to evaluate the safety and assessment of newly developed coprocessed excipients. The ultimate aim of this procedure is to reduce the risk of using new excipients in pharmaceutical formulations.[51]

APPLICATIONS OF COPROCESSED EXCIPIENTS

Coprocessed excipients can show multifunctional properties without any observed sign of chemical change in the existing or incorporated excipients. For this reason, it could be possible to utilize this versatile excipient in developing solid oral formulations and other formulations such as liquid, semisolid, biological, and parenteral formulations. The applications of coprocessed excipients in these formulations are discussed below.

Oral solid dosage forms

Excipient and tablet manufacturing techniques play a significant role in developing solid oral dosage forms. However, the inherent problem of the native excipients such as flow and directly compressible properties may likely create a barrier in the development of tablets via directly compressible tablets. Lately, the literature studies have shown that most coprocessed excipients have been developed using either lactose or cellulose.[52] Apeji *et al*. have developed and optimized starch-based coprocessed excipients for direct compression tablets using a mixture design. Starch-based coprocessed excipients containing the optimal amount of tapioca starch (90%), gelatin (7.5%), and colloidal silicon dioxide (2.5%) exhibited appreciable multifunctionality compared to native starch concerning the angle of repose Carr's index, Hausner's ratio, compressibility, and compatibility. Directly compressible tablets using these coprocessed excipients satisfied the USP specification and improved the disintegration time and drug release, which is significant compared to Prosolv® and StarLac.[27] Assaf *et al*. prepared the coprocessed excipients containing starch/MCC/chitin as hydrophilic polymers onto magnesium silicate. Characterization studies have shown that magnesium silicate incorporated successfully into hydrophilic polymers improved powder characteristics such as powder flowability, compatibility, and stability. It also enhanced crushing strength, disintegration time, and rapid drug dissolution from the tablet.[22]

Semisolid dosage forms

Semisolid dosage forms are the most significant portion of pharmaceutical products. However, some solid excipients have poor physicochemical characteristics, which decreases the integrity of the final formulations. Therefore, new excipients have been developed to increase the appearance, feel, bioavailability,

and successful administration of the transdermal route. Gelucire is one of the excipients used successfully to prepare semisolid forms. It is generally developed by forming the reaction between PEG and fatty acids; PEG is hydrophilic, while fatty acid shows a lipophilic nature. The combination of PEG and fatty acid with variation in their molecular weight leads to the formation of surfactants, offering a wide range of hydrophilic-lipophilic balance (HLB) values.[53-55] Owing to its exceptional property, Gelucire could act as coprocessed excipients in semisolid preparation. In these dosage forms, Gelucire stabilizes the many semisolid dosage forms like creams, lotion, and gels. It also acts as a thickener and penetration enhancer for the transdermal delivery system. Saxena *et al*. prepared the *in situ* emulgel containing piroxicam with different concentrations of molten Gelucire 39/01 and low viscosity grades of sodium alginate. They evaluated its impact on the anti-inflammatory response. The prepared *in situ* emulgel demonstrated a significant enhancement in the analgesic/anti-inflammatory activity compared to conventional *in situ* gel.[56] Kalpana *et al*. designed and evaluated semisolid lipid matrix (SSM) formulation using various mixtures of Gelucire (i.e., 44/14, 50/13/, 33/01, and 43/01), PEG (4000 and 6000), and poloxamer 188. The SSM formulations containing Gelucire (i.e., 44/14, 50/13/, 33/01, and 43/01) were found to notably enhance the dissolution of Aceclofenac in a sustained manner for up to 24 h.[57]

Parenteral dosage forms

An accurate, precise type and extent of excipients and/or coprocessed excipients in the parenteral formulations must help provide stability throughout their manufacturing to storage conditions. Biological and parenteral formulations are the growing field of formulations. However, its inherent instability may be liable for physicochemical degradation. This stability problem could be solved by the appropriate use of excipients and coprocessed excipients. Compatible excipients are added to biological preparations with a variety of functions. These include increasing the solubility of the active pharmaceutical ingredient (API), enhancing its process and shelf life, preserving the formulations' pH and tonicity during use, preserving the stable confirmation of the protein and vaccine, and lowering the API's degradation and aggregation. Similarly, excipients also act as bulking agents and antioxidants or preservatives.[58] Adjuvant excipients are utilized in vaccination formulations instead of biological ones, and they exhibit or improve the therapeutic impact of API or the added antigen's capacity to activate the human immune system.[59]

REGULATORY CONSIDERATIONS FOR COPROCESSED EXCIPIENTS

Every newly created excipient must have approval for both safety and effectiveness from a number of regulatory bodies. Approvals from the regulatory agencies confirm the excipients industry for its launch into the pharmaceutical market. The process of getting a drug product approved by the FDA begins with the filing of a new drug application (NDA) or an abbreviated NDA application that includes comprehensive information about the active pharmaceutical ingredient (API), different components, and related excipients. The detailed report must include the safety datasheet, composition statement, specification, and use of any sophisticated analytical technique for the assessment of API as well as excipients. Federal laws generally use the safety information of excipients (Drug and Cosmetic Act, 1938) to understand their use in the intended formulations. Apart from toxicological studies of excipients, their pharmacological evaluation must also be evaluated according to the International Conference on Harmonization guidelines. As stated earlier, excipients are substances or groups of importance that provide strong integrity to the final formulations. However, it can be modified scientifically according to the guidelines for combining excipients and their intended use in pharmaceutical formulations. The modification of the existing excipients, i.e., coprocessed excipients, which involves more than two existing excipients at the subparticle level, leads to the formation of single excipients with enhanced multifunctional properties. In addition, it has been stated that there is no chemical change observed during the coprocessing; in fact, it merely shows the physical changes of the incorporated excipients. When there are no chemical changes in the coprocessed excipients, it can be considered safe under the category of GRAS with one condition: if the precise nature is also present in the parent incorporated excipients. Therefore, according to this criterion, there is no need for additional toxicological and pharmacological studies to approve coprocessed excipients. Despite the coprocessed excipients' highest level of safety, the producer nonetheless had a significant issue when it came to adding them to the official monograph. Because of this significant hurdle, the pharmaceutical excipients industry could not make it possible to introduce it into the market. Furthermore, only a small number of coprocessed excipients, including compressible sugar, spray-crystallized dextrose-maltose, and dispersible cellulose, have been officially recognized by the USP-NF and British Pharmacopoeia. Similarly, the newly developed silicified microcrystalline cellulose and Avicel CE15 coprocessed excipients are included in the third edition of the handbook of pharmaceutical excipients.

CONCLUSION

This review concluded that pharmaceutical excipients are essential to modern dosage forms. Inferior issues related to native excipients can be found in the initial weighing, middle, and packaging processes. Adopting the cGMP process in the pharmaceutical industry can somewhat solve this problem. Therefore, there is a strong need to use the alternative approach to overcome the native excipients issues. A multifunctional coprocessed excipient is the most appropriate, suitable, and promising approach to help formulation scientists understand

its advantage and utility in developing various pharmaceutical dosage forms.

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