REVIEW ARTICLE

Synergizing functionality in pharmaceutical applications with co-processed excipients: An updated review

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Abstract

Co-processed excipients (CPEs) are gaining prominence as versatile ingredients in pharmaceutical formulations, offering enhanced functionality by combining the properties of multiple excipients into a single material. This review delves into their preparation methods, such as spray drying, co-precipitation, and agglomeration, which are designed to improve flowability, compressibility, and compatibility. Their applications are discussed in detail, particularly in orally disintegrating formulations, where they play a key role in ensuring rapid disintegration, better mouthfeel, and adequate mechanical strength. In addition, their utility in direct compression for simplified manufacturing processes and for sustained-release formulations to achieve controlled drug release is explored. The review also highlights regulatory perspectives, addressing classification, documentation, and approval challenges associated with these excipients. By connecting formulation science with regulatory requirements, this article emphasizes the critical role of CPEs in advancing pharmaceutical development.

Key words: Co-processed excipient, direct compression, multifunctional excipient, orally disintegrating tablets, sustained-release

INTRODUCTION

The increasing cost of identifying and developing newer drugs or active pharmaceutical ingredients (APIs) has propelled the pharmaceutical research industry to deviate from discovering newer chemical moieties to developing newer formulation technologies to enhance the clinical efficacy of existing drug molecules. Pharmaceutical excipients have been a major driving force responsible for this shift in trend. The "International Pharmaceutical Excipients Council" (2009) defines excipients as substances that are present in a finished pharmaceutical dosage form other than the active drug substance.[1] Excipients are a crucial component of pharmaceutical formulations in that they are present in greater amounts than the API. They play important roles in the formulations by improving the identity, protecting, elevating the stability, influencing drug release and absorption, and enhancing the quality and patient compliance of the API. Excipients must ideally be chemically non-reactive to the API, inert to the human body, and non-toxic.

Oral route is still the most preferred for the administration of dosage forms due to its non-invasive nature, amenability to self-administration, flexibility in the selection of dosage forms, wide availability of excipients, relatively non-complex methods of manufacture, and feasibility to scale-up.[2,3] Tablets and capsules have conventionally been the most common dosage forms administered through the oral route due to the inconvenience and dose non-uniformity associated with liquid formulations. Such oral solid formulations also suffer from numerous drawbacks such as a slower onset of

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action, lower bioavailability, and increased incidence of side-effects due to the peak-valley pharmacokinetic profile, risk and/or fear of swallowing in pediatric or geriatric patients, and a more frequent dosage regimen. However, numerous advances are being explored with the development of tablets and capsules such as mouth-dissolving tablets and sustained-release (SR) tablets. Moreover, the method of compression of tablets has also been simplified with the introduction of "direct compression" process. While such advances may be highly beneficial in improving the quality of tablets, the success of such technologies is highly dependent on the type of excipients employed. Practically, there is a lack of a single excipient that may successfully allow the execution of the aforementioned advances. Furthermore, the development of an entirely new chemical entity and exploring it as a potential excipient is not only time-consuming and expensive but also faces numerous regulatory hurdles.[4] Hence, the onus is on the development of an admixture of two or more currently existing excipients that may offer the necessary functionality. Such admixtures are referred to as "Co-processed excipients" (CPEs). The established co-processing methodologies alter the physical properties of the involved excipients without causing any significant chemical change. The co-processing results in a material with improved functionality while concealing the undesirable properties associated with the individual excipients.

Most of the APIs incorporated in solid oral dosage forms have poor powder characteristics, or are hygroscopic which may present hurdles in the development process. CPEs due to their multiple functionalities facilitate the formulation of such APIs. CPEs aim to physically modify the properties of individual excipients and thereby the API such as flowability, solubility, stability, and compressibility without significantly changing their chemical composition. The goal of using CPEs is to optimize the performance of the final formulation and to potentially reduce the number of excipients needed, thereby reducing complexity of formulation optimization. Co-processing was earlier employed by the confectionary and food industry to enhance stability, solubility, gelling properties, and wettability of food ingredients. The concept of co-processing of excipients was introduced in the pharmaceutical industry in the late 1980s with the advent of "Cellactose (Meggle Co., Wasserburg, Germany)" which is a co-processed combination of 75% cellulose and 25% lactose.[5] The excipients chosen for co-processing should complement each other to conceal the less-appealing properties of individual excipients, while improving the functional properties of the resultant excipient. The ideal characteristics of a CPE are represented in Figure 1. CPEs have significantly improved the formulation and manufacturing of oral solid dosage forms; especially tablets due to their numerous benefits over conventioned excipients and technologies such as significantly improved flow properties and compressibility, streamlined manufacturing process thereby facilitation direct compression (DC) as a suitable alternative to wet granulation, consistency in dose and drug content, enhanced disintegration and dissolution, masking poor sensory attributes, and ensuring regulatory and functional consistency.

This review article aims to discuss the concept, fabrication considerations, and applications of CPEs. Among the various applications employing CPEs, the use of such multifunctional ingredients for manufacturing tablets by "direct compression" method, the fabrication of "orally disintegrating tablets," and formulation of "sustained/extended" release tablets shall be discussed in detail.

IDENTIFICATION AND SELECTION OF EXCIPIENTS FOR COPROCESSING

Selection of excipients for co-processing is not recommended to be done randomly but must be done carefully, considering

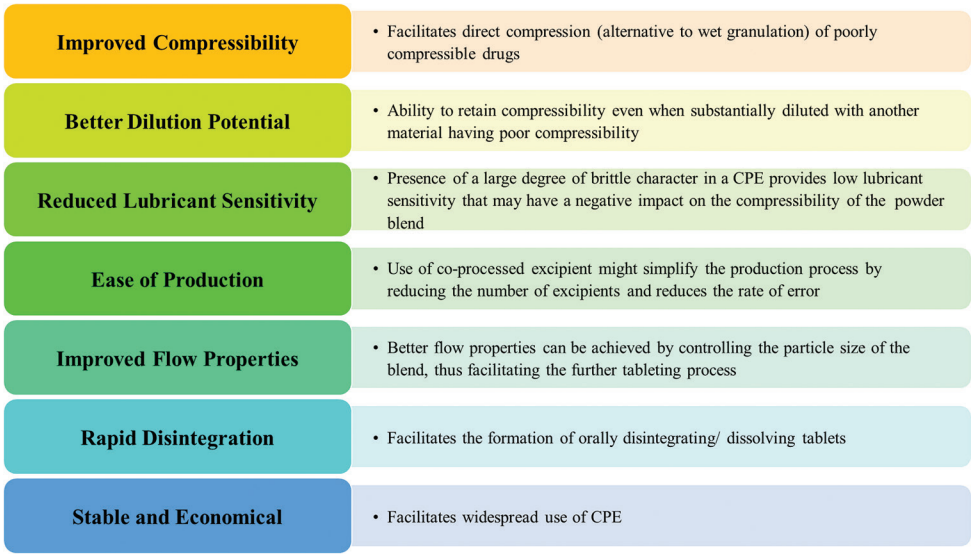

Figure 1: Ideal characteristics of co-processed excipients

the properties of the involved excipients, the properties to be concealed, and the properties desirable in the final developed excipient. A few steps are important to consider when designing a new CPE that satisfies the functional requirement of a specific application.

Selection of the Group of Excipients for Co-processing is Crucial

A well-designed CPE should carefully balance "plasticity" and "brittleness" to eliminate the accumulation of unwanted elastic energy during compression. This will result in a product with minimal stress relaxation and lower tendency of "capping" and "lamination" in the compressed tablets. The chosen combination of excipients should be complementary, working synergistically to achieve the desired properties.

Assessing the Particle Size is of Utmost Importance

Particle size significantly impacts the micromeritics of the end product. In cases where participating excipients have variations in initial particle sizes, the focus should be on producing the final co-processed adjuvant with uniform particle size.

Selection of a Suitable Technique to Co-process Various Excipients is Critical

There are numerous methods available for co-processing such as wet granulation, melt granulation, freeze drying, spray drying, and hot melt extrusion. The method selected for co-processing has a significant impact on the quality of the final product. Hence, the processing method must be selected vigilantly.[6]

Optimization of the Process and the Proportion of each Excipient is Essential

The proportion of individual excipients can significantly contribute to functionality variations in the end-product. It is thus imperative to employ various optimization techniques and experimental designs with sound statistical analysis to obtain a final product with the desired functionalities.

METHOD FOR MANUFACTURING EXCIPIENTS

Various methods used for coprocessing excipients are depicted in Figure 2. The method selected for co-processing has a significant effect on the final product quality. Hence, the processing method must be screened vigilantly.

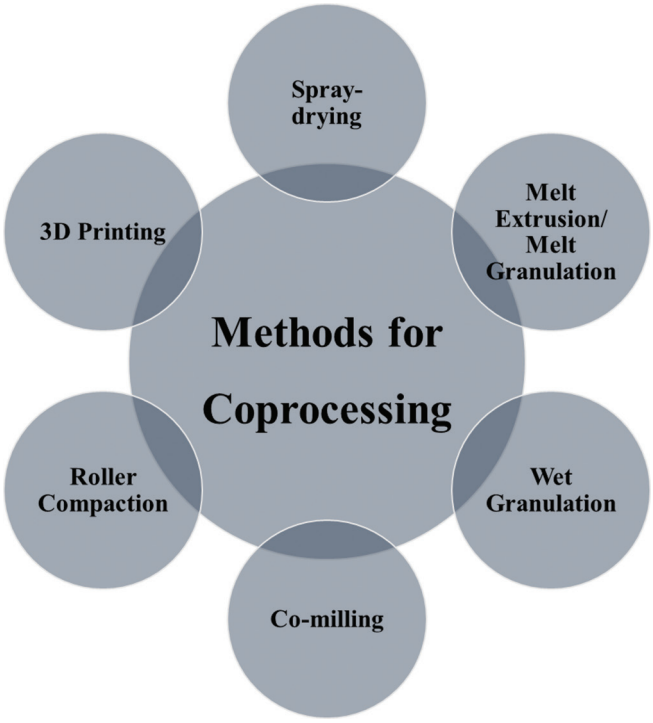

Figure 2: Methods for manufacturing co-processed excipients

Spray-drying

Spray drying is a process that converts feed from a liquid state such as solution, suspension, dispersion, or emulsion into dried particles in the form of powders, granules, or agglomerates.[7] This technique functions as a continuous particle drying process. In co-processing applications, individual excipients are dissolved or dispersed in a common solvent and then spray-dried to produce the final product in the form of a fine, dry powder. Some advantages of spray drying as a method for co-processing include its amenability to be run as a continuous process, feasibility to handle labile ingredients, and the resultant product is known to have significantly improved flow properties and enhanced compactibility that results in an increased tableting speed. Chauhan *et al*. developed a CPE composed of 30% microcrystalline cellulose (MCC), 25% lactose, and 45% StarCap 1500 by spray-drying method. The developed excipient had excellent flow properties as evident by the results of angle of repose and considerably improved the compressibility of the drug as determined by the parameters of Kawakita's and Kuno's equation and Heckel's equation. The dilution potential was found to be about 40%.[8]

Melt Extrusion

Melt extrusion is a relatively newer method used for co-processing wherein the blend of excipients is melted and forced through a die. The extruded products are then allowed to solidify to form the final product. This streamlined process ensures efficient production and high-quality result. Despite

being unsuitable for thermolabile products, this method is automated and hence convenient and rapid, and has high reproducibility. A lipid based CPE was prepared by *in situ* fluidized bed melt granulation process for suitability in DC process.[9] Lactose monohydrate was fused with glyceryl dibehenate or glyceryl palmitostearate as lipidic meltable binders. Solid-state characterization confirmed the absence of any chemical interactions between the individual components. The final product displayed improved flow properties and better tabletability compared to the individual components.[10]

Wet Granulation

A common and easy technique for creating co-processed adjuvants is wet granulation using either high-shear granulators or fluidized bed granulators.[11] The products formed in high-shear granulators are denser than those obtained in fluid bed granulation. However, both methods result in the formation of CPE with a granular size thereby improving their tableting suitability. Benabbas *et al*. used wet granulation method to develop a CPE composed of alginic acid and MCC. The optimum concentration of 10% alginic acid and 90% MCC when granulated with 70% water in a high-shear granulator yielded a co-processed product with good tabletability, enhanced flow properties, and a significantly faster disintegration time compared to a commercial CPE Prosolv® orally dissolving tablets (ODT).[12]

Co-milling

Various types of milling equipment, including roller mill, ball mill, and hammer mill, can be employed for co-milling carefully selected blend of excipients to generate a multifunctional product. A CPE for DC was prepared by processing a mixture of mannitol and crospovidone (CP) in a ball mill. The resultant product displayed better compatibility and stability of the product compared to a physical mixture of the excipients. The tablets also maintained a tensile strength >1.0 MPa.[13]

Roller Compaction

A roller compactor or Chilsonator is an effective approach for dry granulation methods that are also used to produce granules or dense sheets of CPE.[14] Gangurde *et al*. developed a CPE composed of high-molecular-weight polyethylene oxide and hydroxypropyl methylcellulose (HPMC) using roller compaction method to be used for the fabrication of SR tablets. The developed CPE has superior flow properties and tabletability compared to the individual excipients. The moisture content was found to be <1% and swelling capacity was in the range of 40–50%.[15]

FOCUS AREAS OF APPLICATIONS OF CPES

The following sections discuss the applications of CPE in three major areas of formulation development, that is, DC of tableting excipients, development of orally disintegrating/dissolving tablets, and development of SR formulations.

CPEs Used in DC

Despite the introduction of many novel dosage forms and newer routes of drug administration, tablets remain the dosage form of choice across patients and physicians alike.[16,17] The formulation optimization and scale-up of tablet formulations is often limited by the numerous excipients employed and the multifaceted manufacturing processes. The step of granulation that often precedes tablet compression is either performed using wet granulation involving the addition of a liquid binder or compression granulation which uses the force of compaction for preparing granules. An alternative method, that is, DC involved blending of the solid API with other solid excipients followed by compression. This non-complex approach to compression of tablets has established itself as the preferred method of tablet manufacturing in many pharmaceutical industries. This high-speed technique of production is straightforward resulting in successful and effective tableting operation.[18] It involves preparation of a simple physical mixture of two or more APIs, excipients, and lubricant followed by compression without the need of additional processing procedures.[19] Other methods of granulation such as dry and wet granulation in terms suffer from numerous drawbacks such as stability concerns concerning heat and moisture-sensitive drugs. DC method prevails over all these problems. It is cost-effective as it reduces the number of steps for tablet production and also reduces the chances of microbial contamination which is most common in case of wet granulation method. Furthermore, it prevents stability problems of drugs that are moisture and heat sensitive. DC method also eliminates the chances of wear and tear of punches due to high pressure required for compression of tablets by slugging and roller compaction involved in dry granulation method.[20]

While being extremely convenient, DC warrants the use of directly compressible diluents that possess characteristics such as good pharmaceutical functionality, and rapid disintegration capacity.[21,22] With the advent of high-speed tableting equipment and the use of DC methods for tableting, there is an ever-growing demand on the functionality of excipients. To create a stable excipient with multifunctional activity, coprocessing is crucial.[23] CPEs fabricated for DC are mostly associated with lactose and celluloses; particularly MCC. Lactose, despite being one of the oldest and most commonly used diluent has poor compatibility and suffers from inadequate flow properties.[24] The crystalline alpha-lactose monohydrate has been modified to small

agglomerates (Pharmatose DCL 15) or its spray-dried form that has better flow properties and compactibility. However, the compressibility of spray-dried lactose is not still deemed acceptable. Hence, it was further lent to coprocessing. Combilose is a novel lactose-based co-processed created to overcome the problems related to the manufacturability of lactose. A detailed study focusing on various granulation techniques of lactose showed that freezing followed by drying of lactose with an aqueous dispersion of starch can enhance compressibility and exhibit lower ejection forces. An aqueous dispersion of maltose monohydrate and maize was overnight refrigerated, then heated to 60°C to facilitate pre-gelatinization of starch, followed by drying in a tray dryer for a shorter period. The different batches of Combilose exhibited fair to excellent flow properties. The tablets compressed with Combilose also exhibited higher values of tensile strength and bonding index. Results obtained from the dilution potential and lubricant sensitivity of Combilose demonstrated that Combilose with an increase in the percentage of maltose provides a better dilution potential, which, however, exhibits high sensitivity for hydrophobic lubricants such as magnesium stearate which led to capping and lamination of resultant tablets.[25] The above case-study thus proves that the compressibility of an excipient like lactose could be improved by treating plastically deforming material such as pregelatinized starch. Another lactose-based CPE developed by spray drying, comprised α-lactose monohydrate (a filler), HPMC E3 (a binder), and polyvinylpolypyrrolidone (PVPP) (a superdisintegrant) to enhance the compression qualities of lactose. The properties of CPE were influenced by the grade of lactose grade, percentage of HPMC, and percentage of PVPP. The developed excipients were evaluated for various micromeritic properties. An increase in percentage of HPMC or the primary size of lactose demonstrated significant enhancement in the compatibility of excipients. The addition of 3.5% of PVPP had a minute effect on compatibility, but significantly improved the disintegration ability.[26]

MCC was found to have relatively better flow and low hygroscopicity. However, due to a phenomenon referred to as "quasi hornification," MCC loses its compressibility when incorporated in wet granulation. The flow property of MCC is also poor when compared to other DC diluents due to its smaller particle size. Co-processing of MCC with silicon dioxide yielded Prosolv which showed improved strength of tablet compacts and less sensitivity to wet granulation. Sugars and polyols were also considered to be potential candidates for DC diluents. Sorbitol and mannitol are commonly used as diluents for chewable tablets due to their sweet taste and superior mouth-feel. However, the hygroscopic nature affects the resultant tablet's hardness, disintegration, and dissolution. Compressol S, a directly compressible excipient consisting of sorbitol and mannitol, is significantly less hygroscopic than sorbitol. Another CPE comprising xylitol and sodium CMC is Xylitab which is marketed as a directly compressible diluent due to its ideal compaction profile, flowability, lubricity, and dilution potential.

Jacob *et al*. developed a CPE consisting of MCC and mannitol fabricated by spray drying technique as a directly compressible excipient to develop a fast-dissolving tablet formulation. The CPE was prepared by passing both MCC and mannitol through a fine sieve to form composite particles in various mixing ratios. The developed excipient was evaluated for their tableting suitability. An increase in the percentage of MCC enhanced the compressibility of the developed CPE, although a decrease in the fluidity of the composite particles was observed. Although, MCC and mannitol are both widely used in fast-dissolving tablets, the resultant CPE has a slower dissolution due to the non-wetting property of the compact inner core.[27]

A combination of hydrophilic and lipophilic excipients may also serve as potential candidates for DC. In a study published by Medarević *et al*., lactose monohydrate was co-processed by fluid-bed melt granulation with addition of hydrophilic (PEG 4000 and poloxamer) and lipophilic (glyceryl palmitostearate) melt binders. These melt binders were added to improve the compression properties of lactose monohydrate. The CPE presents superior flow properties, better binding function, self-lubricating properties, and better throughput compared to the commercial "Ludipress®." Coprocessing of Lactose monohydrate with 20% poloxamer 188 and 20% PEG provided tablets with satisfactory tensile strength and good lubricating properties over a wide range of compression pressures. However, the lubricating properties significantly improved when glyceryl palmitostearate was added.[28] Table 1 illustrates some examples of commercially developed CPEs for DC.

CPEs Used in Orally Disintegrating/Dissolving Formulations

Orodispersible or orally disintegrating tablets or ODTs are those that disperse/dissolve rapidly after being placed in the oral cavity.[35] European pharmacopoeia (EP) describes ODTs as tablets that disperse in less than 3 min in the buccal cavity before being swallowed.[36] The resultant solution/suspension of the drug in saliva is then ingested by the patient. ODTs are extensively researched as a convenient oral solid dosage form for pediatric and geriatric patients who are unable to swallow tablets or fear the same due to the risk of choking. Such formulations are also pursued by patients suffering from dysphagia which implies difficulty in swallowing.[37,38] ODTs are also significant in the lifecycle management of many obsolete or currently existing drugs since they present a newer approach to the formulation of such drugs.[39,40] The rapid disintegration of ODTs is attributed to the presence of a porous structure within the tablet matrix compressed at lower compression pressure, or the inclusion of superdisintegrants that possess the ability to swell rapidly even in presence of low volumes of saliva. Such specialized excipients yielding a robust tablet at lower compression force while also offering rapid disintegration can be developed by coprocessing.

Table 1: List of commercially available co-processed excipients for direct compression[9,27,29-34]

Excipient combination	Brand name	Method of processing	Remarks
Microcrystalline cellulose (MCC) 90%, Mannitol 10%	Avicel® HFE 102	Spray drying	Better flow properties, Exhibits better tableting at slower tableting speed, Designed for direct compression, Less sensitive to lubrication.
Sucrose-Invert Sugar	SUGARTAB®	Co-crystallization	Better flow properties used for direct compression of tablets, good taste masking characteristics, better chemical stability, less hygroscopicity, used for developing vitamin formulations which have compression problems.
Lactose (85% lactose monohydrate), maize starch (15% native maize starch	StarLac®	Spray drying	Super disintegrant, Filler/binder, high flowability, direct compression, good compactility, and better for roller compaction than MCC as it generates less dust during milling of resulting ribbons.
Mannitol (70%), Sorbitol (30%)	Compresol®	Hot-melt Extrusion	300% less hygroscopic than sorbitol do not have sticking problems during tableting, suitable for moisture sensitive formulations such as orally disintegrating and chewable tablets.
β-Lactose and anhydrous lactitol	Pharmatose® DCL 40	Spray drying	Good flowability, designed for direct compression, high compatibility.

Besides accelerating the process of disintegration, CPE also improves the wettability of the formulation, and provides superior tabletability. They also enhance rheological characteristics by modifying viscosity, resulting in rapid tablet disintegration and prompt therapeutic action. The use of CPE in orodispersible formulation expels the need for any additional excipients or lubricants which reduce the time and expenditure associated with the production of ODTs.

In a study cited by Brniak *et al*., evaluation of three different CPE for ODTs, that is, F-Melt C (dibasic calcium phosphate anhydrous), Pharmaburst (sugar alcohols, croscarmellose and CP, silicon dioxide), and Ludiflash (D-Mannitol, Kollidon polyvinyl acetate, and povidone) were compared.[41] Ibuprofen, a non-steroidal anti-inflammatory drug used to reduce pain, fever, and inflammation was selected as the model drug. Herein, ODTs of Ibuprofen were prepared by DC method. These tablets were prepared using different compression forces. For ODTs prepared using F Melt C, the thickness of the tablets compressed at 10 kN and 15 kN was found to increase. The ODTs then rapidly disintegrated within 5–20 s due to rapid wetting and swelling. In case of ODTs compressed at 20 kN, the disintegration time was found to be greater. The ODTs compressed with Ludiflash exhibited swelling for 5–10 s, and then, the ODTs gradually disintegrated. In case of Pharmaburst containing ODTs, the thickness of the tablets compressed at 10 kN and 15 kN reduced over a period and then the ODTs disintegrated. For Pharmaburst ODTs compressed at 20 kN, no change in the thickness of the tablets was observed and the tablets started disintegrating gradually over a period. The study eventually concluded that the disintegration time of ODTs increased with the compression force when compressed using CPE.

In a study cited by Pituanan and Surini, a CPE was developed using pregelatinized cassava starch (PCS) and gum acacia. ODTs of Gingerol were prepared incorporating the resultant CPE by DC method. The resultant excipient exhibited superior binder, filler, and disintegrant properties. The prepared tablets contained PCS and Acacia in ratios ranging from 5:5 to 9:1. The disintegration time of the tablets was found to be significantly influenced by the swelling index of the excipients in the medium. At 5 min, the swelling index of all tablets was also almost uniform. However, after 2 h, tablets containing PCS: Acacia in a ratio of 9:1 had the highest swelling index. This ratio was thus considered to be ideal when using this CPE as a disintegrant. Gum acacia is known to have lower water absorption properties as compared to PCS; hence, the composition containing a greater concentration of PCS was found to have a higher swelling index and facilitate rapid disintegration of tablets.[42]

In another study published by Conceição *et al*., carbamazepine was used as the model hydrophobic drug and Hydroxypropyl-Beta-Cyclodextrin as a solubilizer. The ODTs of carbamazepine were prepared using CPEs such as Prosolv ODT G2 (mannitol, MCC, CP, fructose, and colloidal silicon dioxide) and F-Melt Type C (mannitol, MCC, CP, xylitol, and anhydrous dibasic calcium phosphate).[43] Six different samples of ODTs with different ratios of CPEs were prepared by DC method. Both Prosolv and F-Melt Type C consist of CP which is an excellent superdisintegrant that enhances the tablet disintegration properties by mechanism of swelling. Daraghmeh *et al*. developed a CPE composed of chitin and mannitol to develop rapidly dissolving tablets of salbutamol sulfate, a fast-acting bronchodilator by DC method. The tablets were prepared using three different ratios of chitin and mannitol wherein the ratio 20:80 was found to be the optimal as this formulation displayed the shortest disintegration time

and wetting time. The presence of mannitol accelerated the disintegration and dissolution of ODTs due to which the formulation containing higher proportion of mannitol displayed fastest disintegration.[44]

In a study cited by Ashoor *et al*., ODTs of finasteride were prepared using combination of superdisintegrants such as croscarmellose sodium (CCS), CP and sodium starch glycolate (SSG).[45] DC method was used for preparing the ODTs which were then evaluated for disintegration time. It was noted that disintegration process was rapid in formulations containing a blend of SSG, CCS, and CP due to their synergistic mechanism that aids in rapid disintegration and dissolution of the tablet. CP facilitates disintegration by wicking mechanism, while SSG and CCS function by swelling. The tablet formulation that comprised CP alone showed a delay in the disintegration profile. Ochoa et al. developed ODTs using a novel binder jet 3D printing technique using CPEs such as GlaenIQ (granulate of isomalt derived from beet sugar), Ludiflash (D-mannitol, CP, polyvinyl acetate, and povidone), and Pharmaburst (mannitol, sorbitol, silicon dioxide, and CP) and found the evaluated CPEs to be compatible with the 3D printing method of tablet manufacturing.[46] Table 2 depicts illustrations of development of orally dissolving dosage forms assisted by CPEs.

CPEs Used in SR/Controlled Release (CR) Formulations

SR or CR formulations that are programmed to release the drug for an extended period are being extensively explored as an approach for improving patient compliance by reducing the frequency of dosage form administration associated with immediate-release formulations. Such dosage forms are also instrumental in lowering the drug-related side-effects by minimizing the fluctuations in the plasma level, thereby also improving the bioavailability of the API.[54] SR formulations necessitate the use of matrix-forming polymeric excipients such as HPMC, chitosan, Eudragit, and polyethylene oxide.[55] Such polymers if synergized with the other tableting excipients such as diluents, glidants, or lubricants, the resultant product can expedite the process of formulation and optimization of SR formulations.

In a study cited by Patel *et al*., a CPE composed of glyceryl monostearate, dicalcium phosphate dihydrate, and polyvinylpyrrolidone K30 was fabricated to facilitate SR. Tramadol hydrochloride, a centrally acting analgesic belonging to BCS Class I, was selected as the model drug. Oral administration of Tramadol requires a dose of 50–100 mg to be taken every 4 h; hence, the need for a SR dosage forms of the drug. Coprocessing was done by the wet granulation method. The CPE was then blended with the drug and magnesium stearate as a lubricant and compressed into the final tablet. The dissolution profile of the compressed tablet was evaluated in comparison with that of the innovator; TRD CONTIN SR 100. The prepared tablets were found to possess acceptable pharmaco-technical properties. The optimized batch of tablets showed a release of 75% within 12 h which was comparable to that of the innovator product. The similarity factor (f2) between the optimized formulation and the innovator was found to be 73.22 and difference factor (f1) was found to be 4.73. This proves the multifunctionality of co-processed glyceryl monostearate and dicalcium phosphate dihydrate, thereby improving the tableting suitability and facilitating SR of a highly water-soluble drug.[56] In the study cited by Biswal *et al*., a combination of Eudragit S-100, medium molecular weight HPMC, and colloidal silicon dioxide was processed to develop a multifunctional excipient for facilitating SR of Quetiapine fumarate, a water-soluble drug used for treatment of schizophrenic patients with a

Table 2: Literature review of co-processed excipients developed for formulating ODTs[34,47-53]

Excipient combination	Method of processing	Remarks
MCC, Mannitol, Aerosil	Spray Drying	Reduced disintegration time, Fast dispersion of tablet in oral cavity.
MCC, Mannitol	Spray Drying	Drug disintegration was increased, stability and dissolution rates were enhanced and better micromeritic properties.
Chitosan, Aerosil	Co-precipitation	Compression behavior and flow properties were enhanced.
Lactose, Mannitol	Melt Granulation	The disintegration time was reduced and flow properties were increased.
MCC, Crospovidone, SiO_2	Spray Drying	Better compactibility, disintegration time was decreased and increased flowability.
Sodium Starch Glycolate, Mannitol	Solvent Evaporation	Disintegration time and wetting time was reduced, flow properties were improved.
MCC, Lactose, Polyvinylpyrrolidone, Polyethylene glycol	Melt Granulation	Decreased disintegration time and better flow characteristics
MCC, Dicalcium Phosphate	Wet Granulation	Better friability, disintegration time and crushing force.

ODT: Orally dissolving tablets, MCC: Microcrystalline cellulose

short life of 6 h which necessitates frequent administration. The CPE was prepared by solvent evaporation method using a rotary vacuum evaporator. The optimized SR tablet was evaluated by United States Pharmacopeia (USP) type II dissolution apparatus (paddle stirrer) at 75 rpm, compared with the tablet prepared using Avicel PH102. The three optimized formulations showed a cumulative release of 97.5%, 98.4%, and 99.3% over 24 h. The developed CPE was thus capable of sustaining the release of a highly water-soluble drug.[57]

Preetha *et al*. published a study that described a CPE prepared by melt granulation method incorporating HPMC and MCC (6:4) to develop a SR formulation of Verapamil HCl. Verapamil HCl is a calcium channel blocker used for the management of hypertension and angina. Verapamil also has a short half-life of 3–8 h which makes it a suitable candidate for a SR profile making it a more patient-compliant formulation. Other excipients added in the tablet were stearic acid, cetostearyl alcohol, guar gum, lactose, sugar, and maize starch and the tablets were compressed by DC method. The *in vitro* release profile of the resultant formulation with the optimized CPE studied using a USP Type II dissolution apparatus revealed that, the resultant product released 99.09% of the drug over 24 h. This release profile was comparable to that of the marketed formulation Verelan PM.[58] In another report published by Ayyappan *et al*., povidone and glyceryl behenate were processed by hot-melting and coprecipitation method and incorporated to develop a SR formulation of gliclazide, a hypoglycemic agent. The resultant formulation containing the co-processed combination yielded a highly efficient SR matrix forming agent to sustain the release of gliclazide. Glyceryl behenate, a hydrophobic excipient which is commonly known, acts as a matrix forming agent in SR formulation exhibited a lowering of its hydrophobicity when co-processed with the hydrophilic povidone. The resultant product possessed an enhanced flow-property which extends the application of this excipient to DC as well. When evaluated in a USP paddle-type dissolution apparatus against the reference product Glizid MR 30, it was found that the optimized batch of tablets showed a release to about 89% within 12 h which was comparable to that of the marketed product. The similarity factor (f2) between the optimized formulation and Glizid MR 30 was found to be 70.91 and the difference factor (f1) was found to be 7.08. This proves the multifunctionality of the CPE, which improves the powder processability of the blend besides facilitating SR of the drug.[59] Table 3 enlists a few more examples of development of modified release formulations assisted by CPEs.

REGULATORY CONCERNS/REGULATORY PERSPECTIVES

The development and use of CPE in pharmaceuticals face numerous technical and regulatory challenges due to the lack of specific guidelines for the same and the complexity of their approval compared to single excipients.[60] Unlike single-component excipients, monographs of CPE are scarcely found in USP or EP. In the absence of a defined monograph, establishing uniform quality standards for such excipients becomes challenging. Manufacturers that choose to use such excipients may need to perform additional testing and set specifications to ensure that the CPE meets the necessary safety and quality requirements for regulatory submission.[61] Regulatory agencies, such as the USFDA or EMA, do not have a clear, distinct approval process for CPE. In general, excipients are approved as part of the drug formulation rather than being individually assessed, meaning that the safety and efficacy of an excipient must be evaluated apropos to a specific formulation. This, however, delays the approval for new excipients and restricts their broader use in future formulations.[62,63]

Being new combinations of approved individual excipients, the regulators may require extensive safety and toxicological data to ensure the safety of the combination, even if the individual components contained therein are well-known and approved. Compiling the necessary toxicology data for CPEs may require extensive *in vitro* and *in vivo* testing, which increases time, cost, and complexity for developers. Moreover, the developers need to prove that no new or unexpected toxicities arise from the method of coprocessing. It is also crucial for CPEs to demonstrate stability and compatibility with the APIs and other formulation components. However, the new physicochemical properties arising from coprocessing can complicate stability testing and may require extended studies.[64] Regulatory bodies are generally cautious when approving new excipient combinations, especially if the excipient performs multiple functions (e.g., filler, binder,

Table 3: Co-processed excipients explored for SR/CR formulations[4,15]

Excipient combination	Method of processing	Remarks
Chitosan and Eudragit S-100	Solvent evaporation method	Increase flow property, compressibility, and dilution potential.
Polyethylene oxide (Polyox® WSR 301) and hydroxypropyl methylcellulose (Methocel® K4M)	Roller compaction technique.	good physico-chemical properties
Hydroxypropyl methylcellulose (HPMC) an sodium carboxymethylcellulose (NaCMC)	Solvent Evaporation Method.	Reduces risk of segregation during tableting, used for controlled release.

SR: Sustained release, CR: Controlled release

and disintegrant). There is a perception of risk if the excipient has not been widely used or tested in similar formulations before. The multifaceted functionality of CPEs may require additional data to support their use in various formulations, especially if they affect critical quality attributes such as disintegration, dissolution, or mechanical strength.

Formulators may be required to submit substantial evidence of the functionality, safety, and performance of the CPE in various drug products, making it difficult to introduce novel CPEs into the market. CPEs often involve processing a blend of excipients by either granulation, extrusion, co-milling, or a co-drying process making their manufacturing process a complex frame-work. This often raises concerns over batch-to-batch consistency of the manufactured CPE. Regulatory agencies may demand stringent controls to ensure that the CPE maintains uniform quality and performance across production batches.[27,65] Regulatory standards and requirements for excipients vary between regions. This lack of harmonization can result in delays when acquiring approval for CPEs in multiple markets, leading to a very tedious, labor-intensive and expensive regulatory process. The use of CPEs in generic drug products can be particularly challenging because the FDA and other agencies often expect generic formulations to closely mimic the reference listed drug or the innovator in excipient composition. Attempting to use a novel CPE in a generic formulation could potentially raise concerns regarding bioequivalence, further exacerbating the evaluation and documentation load. Some CPEs are protected by patents, making them proprietary to certain manufacturers.[66]

The IPEC has however been playing a crucial role in the regulatory approval and standardization of CPEs. The "IPEC Guide for Pharmaceutical Excipients Composition" helps manufacturers define and rationalize the composition of CPEs while the "IPEC Excipient Qualification and GMP Guides" provide a risk based approach for evaluating the safety and quality of excipients. The IPEC also provides a framework for distinguishing physical blends of excipients and CPEs, while also providing guidelines for toxicological risk assessment of CPEs despite established safety guidelines for individual components. IPEC also advocates and raises awareness on the benefits of CPEs, thereby promoting global harmonization of excipients evaluation. Excipients Information Packages are being drafted that provides manufacturing information, functional data, safety/toxicity data, and GMP compliance of CPEs that facilitate the inclusion of CPEs by formulators in the absence of official monographs.

CONCLUSION

CPEs represent a significant advancement in pharmaceutical formulations offering enhanced properties such as improved stability and performance, improved compatibility, enhanced compressibility, controlled disintegration time in case of SR or CR formulations programmed to release the drug for an extended period, and also for orally disintegrating tablets that disperse or dissolve rapidly after being placed in the oral cavity. This strategic combination of excipients not only optimizes the performance of APIs but also streamlines the manufacturing processes. Coprocessing plays a crucial role in the development of a stable excipient with multifunctional activity. Further, coprocessing solves the issues relating to pre-compression parameters, palatability, disintegration time, dissolution time, and sticking which conventional individual excipients might have. Therefore, further research should focus on exploring new combinations, understanding the mechanism of action, and ensuring regulatory compliance to fully harness the potential of these innovative materials.[67,68]

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