https://doi.org/10.31925/farmacia.2024.5.2 **REVIEW**

ADVANCES OF CO-PROCESSED EXCIPIENTS: APPLICABILITY AND FUNCTIONAL CHARACTERISTIC IMPROVEMENTS

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Abstract

The formulation of drug dosage forms is hindered by the scarcity of ideal single-component excipients essential for achieving excellent performance. This necessity requires modification of excipients to improve its functionality and applicability, thereby supporting the manufacturing of dosage forms. One of the effective strategies to develop the excipient is through co-processing two or more excipients, which is classified as physical modification to improve excipients functionality properties with complex interaction that does not occur at simple physical mixture. The physical interaction between those excipients occurs at the sub-particle level, promoting the alteration of bulk properties without significant chemical changes. Co-processed excipients result in superior or multifunctional qualities that provide advantages in drug development phase proven by recent scientific studies. Therefore, advancements of co-processed excipients with better pricing are considered valuable to fulfil the increasing demand for low-cost excipients for generics and the growth of novel dosage forms in the future. Consequently, the prospect of co-processed excipients will still be focal point of research in academics and application in industries since the use of these excipients reduce formulation complexity in the drug development and manufacturing phase.

Rezumat

Lipsa excipienților monocomponenți, esențiali pentru obținerea unei performanțe terapeutice optime, face ca formularea formelor de dozare a medicamentelor să fie o provocare. Prin urmare, este necesară modificarea excipienților pentru a le îmbunătăți funcționalitatea și aplicabilitatea, sprijinind astfel fabricarea formelor de dozare. Una dintre strategiile eficiente de dezvoltare a excipienților este co-procesarea a doi sau mai mulți excipienți, interacțiune fizică ce are loc la nivelul subparticulelor, ceea ce permite modificări minore ale proprietăților fizice, fără efecte chimice semnificative. Studiile științifice recente au demonstrat că excipienții co-procesați capătă calități superioare sau multifuncționale, care oferă avantaje semnificative în faza de dezvoltare a medicamentelor. Abordarea excipienților co-procesați rămâne un subiect de interes în cercetarea și dezvoltarea de medicamente, atât în mediul academic, cât și în industrie, datorită costului scăzut de producție și al faptului că reduc dificultățile întâmpinate în etapa de formulare a medicamentelor.

Keywords: Co-processed excipients, excipients modification, multifunctional excipient, functionality improvement

Introduction

Excipients are essential components in the formulation of drug dosage forms which determine their roles in drug functionality, stability, safety and productibility [1, 2]. However, only slight pharmaceutical excipients fulfil the criteria for being considered ideal. Modification of excipients to improve their functionality can be carried out chemically and physically by developing new grades of existing excipients. Generally, new excipients can be obtained in several development schemes, such as single-modified, novel and co-processed excipients [3]. The development of single-modified excipients entails altering the physical characteristics, resulting in their limited functionality due to a restricted range of possible modification. Compared to physically modified excipient, chemically modified excipients involve alteration of chemical structure through the addition or elimination of functional groups and cross-linking reactions. However, the development of chemically modified excipients is hindered due to the usage of toxic chemical agents such as crosslinker, solvent and catalyst, which potentially leaves residue as poisonous impurities, that requiring additional purification processes and toxicology studies to justify safety usage towards human consumption [1]. Combination of existing excipients through co-processing is an excellent strategy to enhance functionality and achieve the desired performance. Co-processing is a widely studied and commercially used physical modification method for developing new excipients with superior performance compared to its parent excipients resulting in products with synergistic interaction [3]. This technology entails fusing two or more pharmaceutical excipients to develop superior excipients over the comprised materials without any chemical changes [2]. The "co-processing" term also differs from physical mixture, since co-processing entails physical interaction that cannot be achieved through simple mixing [3].
Co-processing technology was previously applied in the food industry to improve characteristics such as

wettability, stability, gelling properties and solubility of food stabilizers [4, 5]. In the pharmaceutical industry, co-processed excipients have been developed to improve characteristics related to flowability and compressibility, to facilitate the direct compression tableting process. Advancements in co-processed excipients enhanced excipient applicability due to improved functionality through a synergistic combination of different superiority properties from various excipients while masking unwanted features [6]. Co-processed excipients can reduce manufacturing costs due to its capability of achieving higher process efficiency with superior functional properties. In addition to functionality improvement, implementing co-processed excipients reduces the need for multiple ingredients in formulation which achieved through the use of a single excipient, effectively reducing the number of excipients during formulation [2]. Co-processed excipients exhibit superior properties while maintaining their chemical configuration proven by similar physicochemical properties characterised using Fourier-Transform Infrared Spectroscopy (FTIR), X-Ray Diffractometer (XRD) and Differential Scanning Calorimetry (DSC) [7, 8]. Furthermore, the developed co-processed excipients can also shorten the drug development phase [9].

This review presents recent advances in co-processed excipients through results from previous studies. A detailed literature review was conducted by utilizing key phrases in the literature search such as "co-processed excipients", "development of co-processed excipients", "functionality improvement", "co-processed excipients tablets", "co-processed excipients ODTs", "co-processed excipients granules", "co-processed excipients adsorbent", "co-processed excipients gels". Initial peer review of publications for this article was done from various search engines such as "Google" and "ScienceDirect" in various research articles from 2013 to 2023, with a few selected earlier articles.

Development of Co-processed Excipients

The main phases of co-processed excipients development include excipient screening, manufacturing process, product formula and process optimization, as presented in Figure 1.

The screening stage involving pre-formulation study based on its functionality characteristics. Typically, the ideal excipients selected are also sustainable and economically available. Most developed excipients usually came from gum-based materials, starch, cellulose-based materials and sugar-based materials. Additionally, assessment and selection of the suitable manufacturing method are carried out according to the material characteristics. The next step is optimization of ratio of parent excipients that provide preeminent functional characteristics for the application [3, 4].

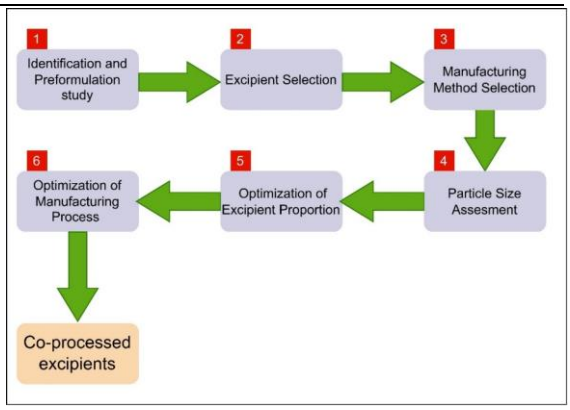

Figure 1.
Flow diagram of co-processed excipients development

Particle Engineering as Co-processed Excipients Conceptual Framework

Modification of excipients requires understanding the properties of solid material, which can be distinguished on three levels, namely molecular, particle and bulk levels. Each of these levels is closely associated, where changes in one level are reflected in another group [7]. The scientific framework for modification is established as presented in Figure 2.

The molecular level comprises the re-arrangement of individual molecules regulating polymorphism and the crystallinity state, which directly affects solubility and chemical reactivity. Modulating crystalline structure at the molecular level impacted to alteration to particle and bulk-level properties [2, 7, 9]. Alteration of molecular characteristics can be performed through the crystal lattice arrangement and chemical modification, such as adding functional groups and cross-linking [10].

At the bulk level, particle form an ensemble involving interaction of each particle. Solid-state properties at the bulk level, such as flowability and compressibility related to processing operations for pharmaceutical manufacturing [7]. The bulk level solid properties can be modified by changing interparticle interaction in the bulk state through a simple physical blend of two or more excipients. However, the hindrance in physical blend is the potential of segregation, impacting batch-to-batch variability during the dosage form manufacturing [10].

Particle level properties including shape, size, surface area and porosity, regulates the performance of the pharmaceutical dosage form and affects the bulk-level properties, which influence the interparticle forces between the solid particle and the cohesive/adhesive property of the solids [7]. Alteration of particle-level properties is defined as particle engineering that can be achieved during co-processing without any changes/ minor changes at the molecular level [7, 10]. These changes affect powder flow, compressibility, water absorption and swelling capacity [10]. All these particle

parameter changes are translated into bulk-level properties changes as presented at Table I.

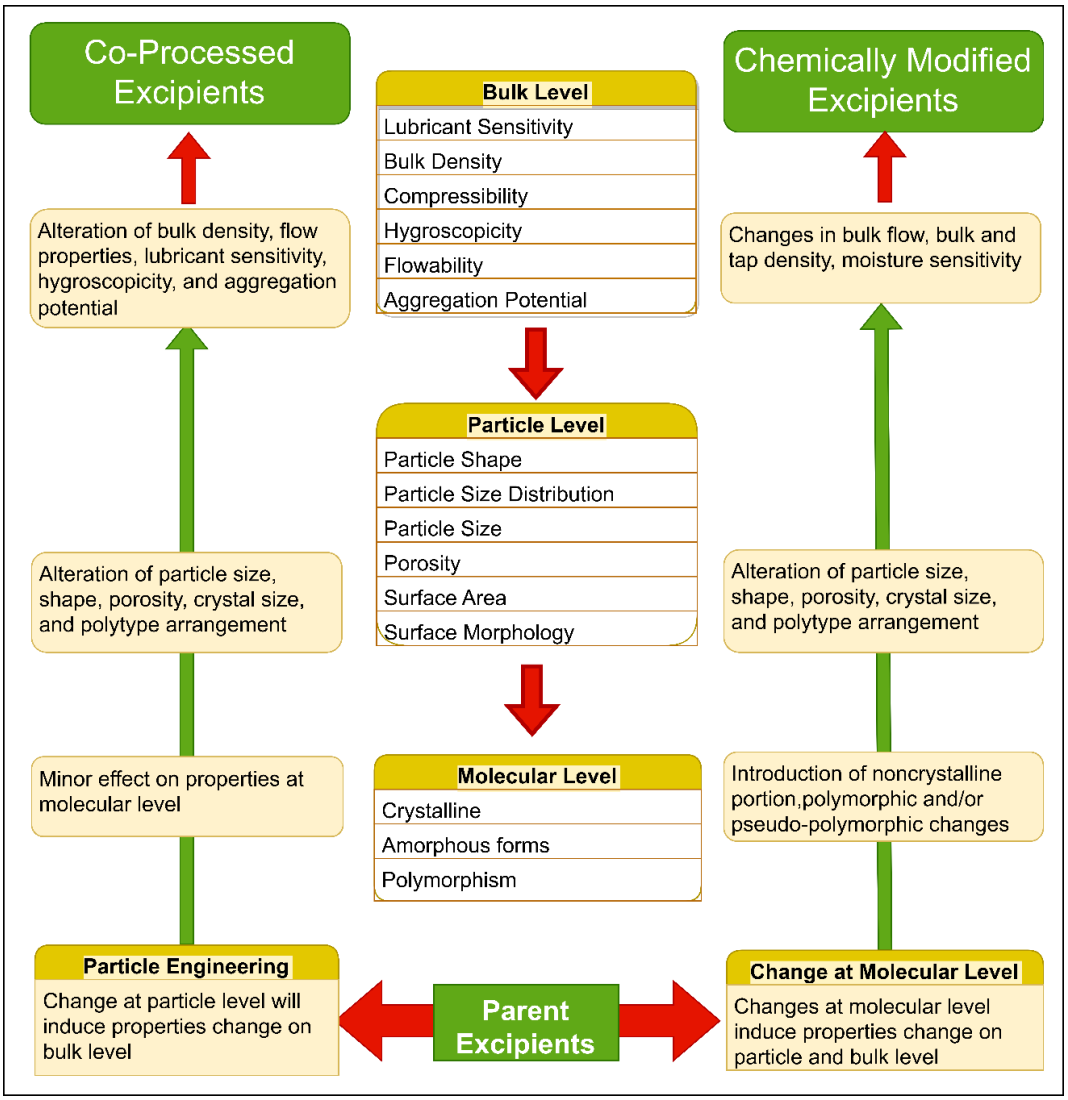

Figure 2.
Three levels of solid-state properties

Table I
Influence of particle parameters to excipient functional characteristics

Name	Affected characteristics
Particle size	Flowability, compressibility
Particle shape	Flowability, compressibility
Particle porosity	Compressibility, disintegratibility
Surface roughness	Flowability, segregation potential, lubricant sensitivity
Size distribution	Segregation potential

Functional properties enhancement of co-processed excipients

Significant improvement in excipients functional properties has been proved to be achieved through co-processing, as showed by several studies [5, 11, 12]. Furthermore, the enhanced functionality including flow properties, lubricant sensitivity, gel strength, compactibility or improved performance such as disintegration profile [13].

Improved flow properties

Controlled particle size, sphere geometry and narrow size distribution improve the flow properties of co-processed excipients. The combination of excipients acting as a single constituent due to co-processing will prevent segregation during the manufacturing process, thus limiting the chance of the dosage form

weight variation. [4, 10]. The flowability of powder is affected by the intra- and inter-particulate forces within particle [14]. The flow of co-processed excipients was perceived better compared to a simple physical mixture that could be disclosed as the impact of co-processing resulting in single constituent particle with similarity in density, size and shape [2].

Several studies have proven improvement of flowability through co-processing. According to Tian *et al*., Lubritose® SD consisting of spray-dried lactose and glyceryl monostearate provided higher flowability showed by the lower angle of repose, elevated Carr's index, compared to its physical mixture [15]. A study by Svačinová *et al*. on F-Melt® showed the influence of particle shape and size distribution on flow properties of co-processed excipients with irregular shape and small particle size showed poor flowing capabilities observed by the high angle of repose value [16]. Enhancement of calcium carbonate flowability was also carried out by Li *et al*. through co-processing with HPMC using spray drying which resulted in great flowability [17].

Improvement of excipients flowability is also affected by the selected co-processing method such as spray drying and granulation. Spray drying equipped with atomization and spherization methods results in spherical particle with smooth surfaces and narrow size distribution, improving flow properties [4, 18]. Furthermore, improvement of flowability through granulation of co-processed excipients has been reported by Benabbas *et al*. in the development of free-flowing granules of alginic acid and MCC [6].

Reduced lubricant sensitivity

Lubricant sensitivity is defined as the potential of interaction between particle during compression disrupted by the addition of lubricant, leading to film formation at particle surface during compression. The lubricant film causes a reduction in the inter-particulate interaction between particle [11]. Low lubricant sensitive excipients prevents the lubricant network by forming a newly exposed surface by fragmentation following compression [11, 18]. Co-processed excipients with low lubricant sensitivity have been developed by Dong *et al*. from HPMC-mannitol and HPMC-calcium carbonate. The results showed that after the mixing process, co-processed excipients had an indication of fragment and deformation under pressure, exposing new areas and halting the form of continuous lubricant film [19]. Co-processed excipients do not always possess better lubricant sensitivity compared to their parents due to the influence of natural properties. StarCap 1500®, a combination of corn and pre-gelatinised starch, showed greater lubricant sensitivity than its parent starch, according to a 2011 study by Mužíková and Eimerová [20].

Enhanced gel strength

Co-processing technology has been extensively used to develop excipients with superior gel strength for modification of the release profile of pharmaceutical dosage forms. Improvement of gel strength through co-processing is caused by assembling an interlaced polymer network when polymer in a dispersed phase is blended together [21]. Therefore, co-processed excipients with improved gel strength can be used as matrix-forming agents for modified-release tablets and hydrogel. Furthermore, their development based on cross-linked amylose and xanthan gum has been carried out by Surini *et al*. and Ariani *et al*., showing improvement in gel strength, which are suitable as matrices for sustained-release dosage forms [22, 23]. A similar trend was also observed by Budaya and Surini, where co-processed excipients of xanthan and acacia gum as matrix-forming agents for famotidine floating gastro-retentive tablets due to high viscosity and gel strength [24]. According to Mughal *et al*., the mix of guar gum, xanthan gum and HPMC as co-processed excipients possess the ability as retardancy agent for sustained release of propranolol hydrochloride [25].

Improved compactibility

Compactibility is the capability of powdered materials to be compressed at a specified strength which determined by the properties of particle [7]. Adeoye and Alebiowu observed that the onset of plastic deformation for mannitol and tapioca starch as parent excipients was lower than the co-processed excipients, showing higher tablet tensile strength. The result concluded that the tensile strength value was dependently reduced due to an increase in porosity and more sphere-like particle shape [14]. Another compactibility improvement was shown by Lin *et al*. in the development of co-processed excipients consisting of lactose-HPMC, lactose-HPC and lactose-PVP for cushioning agent of chlorpheniramine maleate multi-particulates. Based on observations, it was discovered that lactose alone was inferior to co-processed excipients in term of compactibility [26].

Rapid disintegration

Improvement of disintegrability is essential during the formulation of orally disintegrated tablets [27]. Improvement of disintegrability can be caused by the betterment of swelling capacity and wicking properties through higher material porosity [28]. Muzíková *et al*. compared physical mixture of mannitol and MCC with Avicel® HFE-102 as the dry binder. The result showed differences in disintegration time due to the variance in tablet porosity, which regulated the amount of water penetrating the tablets [5].

Manufacturing of co-processed excipients

Manufacturing co-processed excipients can be carried out in several methods, including co-drying, co-crystallization, wet granulation, melt granulation and co-precipitation which significantly impacts their quality and characteristics [29]. Daraghmeh *et al*. investigated the development of co-processed excipients composed

of mannitol and chitin prepared with spray drying, wet granulation and dry blending. The results showed that both physical mixture and dry blending excipients did not improve the compressibility and flowability of material to a sufficient level compared to spray drying and granulation [11]. Dong *et al*. developed co-processed excipients composed of mannitol and HPMC through spray drying and fluid bed coating. The result showed that fluid-bed coated excipients possessed better compaction and lower lubricant sensitivity compared to co-spray drying due to the irregular roughness of particle surface [19].

Co-drying

Co-drying is an economical and environment-friendly method for starch-based excipients. In this method, each excipients dispersion is initially prepared and mixed proportionally at high speed for a long time. Under dispersed conditions, the polymeric chain is disrupted with vast space between each polymeric chain, resulting in a higher potential of entanglement when homogenised. Subsequently, the mixed dispersion is subjected to a drying process known as co-drying. The selection of the drying method is determined by the viscosity properties, where slurry dispersion with high viscosity is usually processed with drum drying, while those with less viscous are subjected to spray drying [30].

Spray drying

Spray drying is an extensively used technology for the development of co-processed excipients [31]. This process includes several steps such as feed atomization, liquid evaporation and powder collection step [32]. The slurry is pumped from the feed container to the drying chamber through an atomization nozzle. Moreover, the solidification of the droplet is occurred when the droplet is contacted with heated air or gas in the drying chamber resulted in spherical aggregates [29, 30, 32]. Additionally, spray drying method provides advantages with the ability to obtain free-flowing particle with lack of organic solvents required [33]. Another alternative to the spray drying method is spray-congealing, a suitable method for meltable materials such as waxes, fatty acids and sugar [33]. Melted compounds will be transformed into tiny droplets with an atomizer which are sprayed into a chamber filled with cold air to promote the solidification process [30].

Drum drying

Drum drying involve formation of a thin film layer on the surface of steel drums filled with heated gases. This method is a suitable option for highly viscous pastes or slurry-like starch-based excipients that are not accommodated by spray drying. Then thin layer films as are subjected to size reduction process into fine excipients powder [34]. However, salt and sugar-based materials are unsuitable for this method due to the difficulty in scraping off from the drum surface. Compared to spray drying, the drum-dried particle possesses irregular shapes, roughness and excellent porosity [35].

Co-crystallization

Co-crystals are solid crystalline which are thermo-dynamically stable due to non-covalent forces that bind co-crystalizing agents together. In this process, the solution is cooled to induce the crystallization process, which consists of nucleation and crystal growth stages, following the decrease of saturated solubility [36]. The nucleation phase induces the forming of crystal nuclei, while the growth stage improves the size of nuclei. Subsequently, these crystals are filtered and washed to eliminate impurities and subjected to a size reduction process to produce the desired particle size [1, 29, 37].

Wet granulation/agglomeration

The agglomeration process involving amalgamation of particle by adding aqueous binder dispersion onto another powder excipients surface [38]. The binder solution acts as a coating agent at the particle surface. Subsequently, the solid bridges keeping the particle intact together are formed by drying process, thereby impacting its particle size, and producing large granule particle. The produced excipients show large particle-sized granules with improved flow properties in accordance with the results by Benabbas *et al*. in the development of co-processed MCC and chitin [39]. One of the advantages of this method is its simplicity and applicability for various excipients [37].

Melt granulation

Melt granulation is a preferred co-processing method for meltable polymer and lipid-based excipients, which is subjected to the heating process above the melting point to promote the transformation of the solid mass into molten form. The blending stage will induce interaction between each material through the application of shear force [40, 41]. Subsequently, the molten mass is extruded and screened to obtain granules with the desired size. The advantages of melt granulation include removing the requirement of solvent and further drying process, the process is quick and continuous, with thermodynamically stable end products [40, 42]. Garg *et al*. applied melt granulation to develop a new multi-functional co-processed excipients composed of the crospovidone as disintegrant, PEG 4000 as binder and calcium phosphate representing diluent [43]. Ćirin-Varađan *et al*. also developed new lactose-based co-processed excipients with meltable binder of glyceryl palmitostearate and glyceryl dibehenate [44]. Melt granulation was also used by Madhvi *et al*. for the development of directly compressible diluent-binders consisting of lactose monohydrate, MCC, mannitol, maize starch and chitin as a diluent, while PEG as binder [45].

Co-precipitation

Co-precipitation has been utilised in pharmaceutical industry to prepare solid dispersion through incorporating one material into another. The material must be in

soluble condition in an organic solvent to facilitate the interaction. The major limitation of this technology is the large amount of organic solvents required, which not sustainable for long-term production [30]. The development of the co-processed excipients by co-precipitation has been done for chitin and chitosan [46]. Rashid *et al*. have successfully developed the chitin-silicon dioxide co-processed excipients through co-precipitation by adding the chitin suspension towards silica to obtain precipitated. The results showed that the co-processed excipients successfully improved the poor flowability and compressibility of chitin [47]. Assaf *et al*. have also successfully developed MCC–magnesium silicate, chitin–magnesium silicate and maize starch–magnesium silicate using co-precipitation method [48]. Another attempt to overcome the same limitations has been made by El-Barghouthi *et al*. with co-precipitated of chitosan-silica which showed improved flowability, compressibility and compactibility [49].

Commercially Available Co-processed Excipients

Co-processed excipients have been developed before for various purposes and role in dosage form formulation. Several commercially available co-processed excipients develop from multiple excipient combinations along with the manufacturing methods used are presented in Table II.

Table II

Commercially available co-processed excipients

Name	Composition	Method	Manufacturer	Ref.
Advantose® FS95	Fructose (95%) and sucrose (5%)	Spray drying	SPI Pharmaceutical (USA)	[29]
Avicel® DG	MCC and dibasic calcium phosphate	Spray drying	Dupont (USA)	[29]
Avicel® CE 15	MCC (85%) and guar gum (15%)	Spray drying	Dupont (USA)	[29, 32]
Avicel® HFE -102	MCC (90%) and mannitol (10%)	Spray drying	Dupont (USA)	[32, 50]
Avicel® RC-591/ CL-611/RC-581	MCC (78 - 95%) and Na-CMC (5 - 22%)	Spray drying	FMC Corporation (USA)	[51]
Cellactose® 80	Lactose monohydrate (75%) and cellulose (25%)	Spray drying	Meggle GmbH and Co. KG (Germany)	[31, 51]
Celocal®	MCC and calcium sulphate	Spray drying	FMC Corporation (USA)	[51]
Ceolous™ RC	MCC and Na-CMC	Spray drying	Asahi Kasel America (USA)	[29]
CombiLac®	Lactose monohydrate (70%), MCC (20%) and corn starch (10%)	Spray drying	Meggle GmbH (Germany)	[50]
Compressol® S	Mannitol (70%) and sorbitol (30%)	Hot melt extrusion	SPI Pharmaceutical (USA)	[29]
Di-Pac®	Sucrose (97%) and dextrin (3%)	Co-crystallization	American Sugar Co. (USA)	[51]
Dipacprosolv®	Sucrose, maltodextrin, MCC and silicon dioxide	Co-crystallization	Penwest Pharmaceuticals (USA)	[29]
F- Melt® Type M	Mannitol (55 - 70%), MCC (10 - 25%), xylitol (2 - 9%), crospovidone (5 - 13%) and magnesium aluminometasilicate (2 - 9%)	Spray drying	Fuji Chemical Industry (Japan)	[50]
ForMa XX®	Calcium carbonate (70%) and sorbitol (30%)	Spray drying	Merck (Germany)	[29]
Granfiller-D™ 211	Mannitol, MCC, croscarmellose sodium and crospovidone	No data	Daicel Corporation (Japan)	[52]
Hisorad®	Mannitol, MCC and croscarmellose sodium	No data	Daicel Corporation (Japan)	[53]
Lubritose™ SD	Spray-dried lactose and glyceryl monostearate	Wet granulation	Kerry (United States)	[15]
Ludiflash®	Mannitol (84 - 92%), crospovidone (4 - 6%), polyvinyl acetate (3.5 - 6%) and povidone (0.25 - 0.6%)	Wet granulation	BASF (Germany)	[29]
Ludipress® LCE	Lactose monohydrate (96.5%) and crospovidone (3.5%)	Granulation	BASF AG (Germany)	[51]
Ludipress®	Lactose monohydrate (93%), PVP (3.5%) and crospovidone (3.5%)	Granulation	BASF AG (Germany)	[31, 51]
LustreClear™	MCC and carrageenan	No data	FMC Corporation (USA)	[51]
MicroceLac® 100	Lactose monohydrate (75%) and MCC (25%)	Spray drying	Meggle GmbH and Co. KG (Germany)	[31, 51]
Nu-Tab®	Sucrose, corn starch and magnesium stearate	Roller compaction	M. B. Sugars Pharmaceutical Limited (India)	[29]
Pan Excea™ MHC 333G	MCC, HPMC and crospovidone	Granulation	Covidien (Ireland)	[29]
Parteck® ODT	Mannitol and croscarmellose sodium	Hot melt extrusion	Merck KGaA (Germany)	[50]
Pharmaburst™ 500	Mannitol (85%), silicon dioxide (< 10%), sorbitol (5%) and crospovidone	Spray drying	SPI Pharma (USA)	[29, 50, 51]

Name	Composition	Method	Manufacturer	Ref.
Pharmaburst ™	Sorbitol–mannitol (84%), crospovidone (16%) and silicon dioxide (< 1%)	Spray drying	SPI Pharma (USA)	[51]
Pharmatose® DLC14	Anhydrous lactose (95%) and lactitol (5%)	No data	DMV (Netherlands)	[31, 51]
Prosolv®	MCC and colloidal silicon dioxide	Spray drying	JRS Pharma (USA)	[29]
ProSolv® SMCC	MCC (98%) and colloidal silicon dioxide (2%)	Spray drying	JRS Group (Germany)	[31, 51]
Ran Explo™ S	MCC (95%) and silica-sodium starch glycolate (5%)	Granulation	RarQ Pharmaceutical (India)	[29]
RetaLac®	HPMC and lactose	Granulation	Meggle GmbH (Germany)	[29]
SmartEx® QD 100	Mannitol, polyvinyl alcohol and HPC	No data	Shin-Etsu Pharma, Nutra and Food (Japan)	[50]
Starcap® 1500	Pregelatinised starch and corn starch	Spray drying	BPSI Holdings, Inc	[29]
Starlac®	Lactose monohydrate (85%) and maize starch (15%)	Spray drying	Meggle GmbH (Germany)	[29]
Timer® X	Xanthan gum (25%), locust bean gum (50%) and dextrose (25%)	Granulation	Penwest Pharmaceuticals (USA)	[29]
Vitacel® VE-650	MCC (65%) and calcium carbonate (35%)	Spray drying	FMC Corporation (USA)	[51]
Xylitab® 100	Xylitol (96.5%) and polydextrose (3.5%)	Granulation	Danisco (Denmark)	[29, 54]
Xylitab® 200	Xylitol (98%) and Na-CMC (2%)	Granulation	Danisco (Denmark)	[29, 54]

MCC – microcrystalline cellulose; Na-CMC – sodium carboxymethyl cellulose; HPMC – hydroxypropyl methylcellulose; HPC – hydroxypropyl cellulose.

Use of Co-processed Excipients

In previous decades, co-processed excipients were initially developed to assist tablet direct compression. However, their applications have been more comprehensive, extending in several types of dosage forms such as tablets, granules, oral disintegrating tablets (ODT), adsorbent and gels [3, 4].

Tablets

The pharmaceutical industry continues to favour direct compression (DC) which require excipient with good powder flowability and high compressibility. These requirements hinder the use of single materials, as only a few possess the qualities. As shown in Table III, several studies have explored the use of co-processed excipients in tablet development, focusing on their role as multifunctional materials acting as diluent, binder, or disintegrant [38].

Composition of the parent excipients affects the properties of the tablet developed. Wang *et al.* reported this phenomenon in the development of multifunctional co-processed excipients composed of lactose monohydrate as filler, HPMC as binder and crospovidone as disintegrant. Furthermore, an increase in the crospovidone ratio led to improved tablet disintegrability and mixture compactibility. The developed excipients showed better compactibility and were superior to commercially available products with the same components, SuperTab® 11 SD and Ludipress® [17].

Table III

Recent studies of co-processed excipients development for tablet formulations

Excipient compositions	Method	Application	Ref.
Lactose, HPMC and PVP	Co-drying	*Gardinia fructus* extract tablet	[17]
Crosslinked carboxymethyl rice starch and silicon dioxide	Co-drying	Placebo tablet	[12]
Acacia gum and calcium carbonate	Wet granulation	Atorvastatin tablet	[55]
Mannitol and chitosan chlorhydrate	Co-drying	Cefuroxime axetil tablet	[46]
Mannitol and chitin	Co-drying, wet granulation and dry blending	Methyldopa tablet	[11]
Mg. silicate and chitin; Mg. silicate and starch; Mg. silicate and MCC	Co-precipitation	Ibuprofen tablet	[56]
Mg. silicate and lactose monohydrate	Roller compaction	Mebeverine HCl tablet; potassium losartan tablet	[57]
Mannitol and MCC	Melt granulation	Placebo tablet	[41]
Alginic acid and MCC	Wet granulation	Placebo tablet	[6]
Mannitol and tapioca starch	Co-drying and dry blending	Paracetamol tablet	[14]
Chitin and calcium carbonate	Co-precipitation	Placebo tablet	[58]
MCC, lactose and starch	Co-drying	Etodolac tablet	[59]
Chitosan, mannitol and crospovidone	Co-drying	Paracetamol tablet	[60]
Dibasic calcium phosphate, PEG 400 and crospovidone	Melt granulation	Aceclofenal tablet	[43]

Excipient compositions	Method	Application	Ref.
Lactose and Poloxamer® 188; Lactose and PEG 4000; Lactose and glyceryl palmitostearate	Melt granulation	Placebo tablet	[42]
Gelatin, tapioca starch and silicon dioxide	Co-drying	Ibuprofen tablet	[61]
Lactose and MCC	Co-drying, wet granulation, co-crystallization	Folic acid tablet	[62]
Dicalcium phosphate dehydrate and MCC	Wet granulation	Hydrochlorothiazide tablet	[63]
PEO and HPMC	Roller compaction	Metoprolol succinate tablet	[64]
Cellulose and silicon dioxide	Co-drying, wet granulation	Placebo tablet	[65]
Lactose, MCC and corn starch	Co-drying	Placebo tablet	[20]
Chitosan chlorhydrate, MCC and mannitol	Co-drying	Cefuroxime axetil tablet	[46]
Lactose, pregelatinised maize starch and sodium CMC	Co-drying	Paracetamol tablet	[66]
Acacia gum and xanthan gum	Co-drying	Famotidine floating tablet	[24]
Acacia gum and cross-linked xanthan gum	Co-drying	Gliclazide sustained release tablet	[67]
Neem gum and lactose, neem gum and rice starch	Co-drying	-	[68]
Lactose monohydrate and glyceryl dibehenate, lactose monohydrate and glyceryl palmitostearate.	Melt granulation	Paracetamol tablet	[44]
Guar gum, xanthan gum and HPMC	Wet granulation	Propranolol hydrochloride	[25]

HPMC – hydroxypropyl methylcellulose; PVP – polyvinylpyrrolidone; Mg – magnesium; PEG – polyethylene glycol; MCC – microcrystalline cellulose; CMC – carboxymethyl cellulose; PEO – polyethylene oxide

Co-processed excipients also aid formulators in developing advanced dosage forms, such as sustained-release tablets through improvement of swelling capacity and gel strength. Surini *et al*. developed a sustained-release gliclazide tablet using co-processed cross-linked acacia with xanthan gums as a filler-binder for the formulation [67]. Other studies by Budaya and Surini used co-processed acacia and xanthan gum as diluents-binder for famotidine floating tablets. These studies showed that co-processing successfully improved the functional characteristics of both gums to be suitable as matrix forming agent [24]. Ćirin-Varađan *et al*. have successfully developed two co-processed excipients composed of lactose monohydrate with glyceryl di-behenate and lactose monohydrate with glyceryl palmitostearate as lipophilic meltable binders using melt granulation [44].

Granules

Excipients play a significant role in determining pellet mechanical properties and performance with several previous development of co-processed excipients are presented at Table IV. The development of co-processed excipients from κ-carrageenan and pectin for manufacturing immediate-release domperidone pellets by extrusion-spheronization method has been carried out by Jade. The formulation was performed by incorporating co-processed carrageenan-pectin, lactose and sodium starch glycolate as binder (20 - 30%), diluent (52 - 62%) and disintegrant (8%), respectively. The studies concluded that the drug dissolution profile depended on the grades of κ-carrageenan and the ratio of κ-carrageenan–pectin [69]. Goyanes and Martínez-Pacheco have successfully developed co-processed excipients (90%) for pellet formulation containing low solubility drugs (10%). The co-dried excipients consisted of MCC, polymethacrylate copolymers, chitosan and sorbitol, which fulfilled the role of diluent-binder-disintegrant for the formulations [70]. The development of co-processed excipients consisting of MCC, gelatinised starch and stearic acid for pellet cushions has been carried out by Li *et al*. to produce tablets containing multi-particulate sustained-release metformin HCl pellets. The result showed that co-processed excipients effectively protected pellets during compression without compromising their disintegrability compared to physical blend cushioning agents at the same composition [71].

Table IV

Recent studies of co-processed excipients development for granules formulations

Excipient compositions	Method	Applications	Ref.
Carrageenan and pectin	Co-drying	Immediate release domperidone pellets	[69]
MCC, gelatinised starch and stearic acid	Co-drying	Cushioning agent for metformin pellets	[71]
MCC, polymethacrylate copolymers, chitosan and sorbitol	Co-drying	Indomethacin, nifedipine, furosemide, prednisolone and hydrochlorothiazide pellets	[70]
Mannitol and HPMC	Co-drying	Metformin pellets	[72]

HPMC: Hydroxypropyl methylcellulose; MCC: microcrystalline cellulose

Orally disintegrating tablets (ODTs)

Orodispersible tablets are potential drug forms intended for paediatric and geriatric consumer or individuals with dysphagia condition. An ideal ODT possesses critical attributes such as great mechanical strength, fast disintegration time and pleasant mouth feel [3]. The use of co-processed excipients in the development of ODT has been previously investigated to aid direct compression tableting process producing tablet with fast disintegration time while maintain adequate mechanical strength.

Soh *et al*. provided an assessment study of commercially available co-processed mannitol with crospovidone, polyvinylpyrrolidone and polyvinyl acetate (Ludiflash®). The results showed that the most preferred formula is 7.5% crospovidone, 1% SiO_2, 87.50% Ludiflash® with additional compounds which possessed rapid disintegration time, low friability and low compression [73]. Furthermore, Kaur *et al*. successfully developed co-processed excipients of crospovidone and MCC (1:1) as binder–disintegrant for tableting of Febuxostat ODT. The developed excipients were accompanied by mannitol as the filler, magnesium stearate and talc as lubricants at the formulation. The results showed significant improvement in tablet hardness, disintegration time and dissolution rate compared to ODT made from physical mixture excipients and commercially available marketed tablet [74]. Lura *et al*. investigated the usage potential of Ludiflash®, co-processed excipients composed of mannitol, crospovidone, povidone and polyvinyl acetate [75].

Comparison of various co-processed excipients in ODT tablet characteristics were done before. Brniak *et al*. conducted a study comparing F-Melts® Type C, Pharmaburst® and Ludiflash® which contain mannitol and crospovidone in development of ODT. Based on the result, it was observed that despite the main compositions of these excipients is similar, the ODTs produced had varying disintegration times as affected by different disintegration properties such as swelling, water wicking and wetting time. F-Melts® Type C which also contain MCC prone to swelling notably prior to disintegration which provide the lowest disintegration time. This type of disintegration was observed similar to Pharmaburst®, while the disintegration mechanism of ODT prepared with Ludiflash® is described as "melting" based on the image of water penetrating into the tablet [76]. Another study by Svačinová *et al*. showed that F-Melts®Type C, F-Melts® Type M and F-Melts® Type F1 had different flow properties, particle size and lubrication sensitivity [16]. Kokott *et al*. explored the potential of commercially available co-processed excipients such as Granfiller-D™, comprising of mannitol, MCC, carmellose, crospovidone and Hisorad® which is composed of mannitol, MCC and croscarmellose sodium with their physical mixture for direct compression of ODT. Comparison of Granfiller-D™ and Hisorad® with their physical mixture resulted in significant smaller tensile strength with increased maximum compression pressure. Although higher disintegration time was observed linearly with increased tensile strength, the value was less compared to the ODT from physical mixture [53].

Adsorbents

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is an advanced solid dosage form which involve transformation of liquid-lipid mix into solid carriers through adsorption incorporating porous silica [77, 78]. Previous studies reported that conventional silica-based adsorbents had an immediate transformation into a gel during their contact with an aqueous medium, clogging the pore, leading to an incomplete release of pre-concentrate [79]. Consequently, silica-based co-processed excipients were developed to improve the material adsorption capacity. Patki and Patel developed co-processed excipients from polyvinyl alcohol (PVA) and calcium silicate (Florite® 100) through a co-drying process. The study showing influence of PVA with higher porosity resulted in greater adsorption capacity promoting rapid emulsification [77].

Gels

The development of hydrogel incorporates the use of a gelling agent, as it determines the gel structure. Surini *et al*. investigated the potential use of co-process excipients consisting of xanthan gum and cross-linked amylose with improved gel strength as a sustained release agent at transdermal hydrogel [22]. Pawar *et al*. patented the usage of co-processed excipients of guar gum–xanthan gum, guar gum–karaya gum and guar gum–ghatti gum as gel forming agent in formulation of sodium diclofenac gel [80].

Jelly, Potential Applications of Co-processed Excipients

One of the new appealing oral dosage forms that can be developed using co-processed excipients is jelly. Jelly provides a sweet-sour taste with a unique shape and chewable texture when consumed [81]. These products can also be developed for geriatrics, paediatric consumers and people with dysphagia conditions [82, 83]. The implementation of jelly as a nutraceutical and pharmaceutical drug dosage form has been investigated as shown in Table V. The critical parameter of a jelly product is chewiness, which correlates with the cohesiveness of the material to maintain its structure when chewed. Consequently, developing hydrocolloid-based co-processed excipients to improve the gel strength is feasible with the combinations based on several gelling agents promote the synergistic effects between each material.

Table V

Previous studies of jelly formulation as dosage forms

Gelling agents	Applications	Ref.
Alginates and carageenan	Instant jelly containing paracetamols beads	[84]
Pectins, guar gum, xanthan gum, tragacanth gum and sodium alginates	Ethylefrine hydrochloride oral medicated jelly	[85]
Gelatine	Vitamin C jelly	[86]
Gelatine and inulin	Rosemary extract (*Rosmarinus officinalis* L.) jelly	[87]
Gelatine and inulin	Propolis extract (*Braccharis dracunculifolia*) jelly	[88]
Gelatine and pectin	*Garcinia atroviridis* puree jelly	[89]
Glucomannan and psyllium husk	Milk permeates and apple puree jelly	[90]

Future Potential and Prospects

Co-processed excipients from certified GRAS, generally recognised as safe, market-available excipients, resulted in low toxicity concerns which categorised as an ideal option for new excipients development [1]. Also, the lack of toxicity concern from the manufacturing process, made the development of co-processed excipients faster and economically feasible, as there were no requirements of several regulatory approval stages for safety and toxicity issues. Consequently, there is a promising future for designed excipients with compliance to performance, quality and safety, as distinguished by an increasing number of research studies and patent cliffs [40].

The development of co-processed excipients in the future should also consider patient acceptability including palatability. Physical characteristics such as particle size and fineness of excipients have a significant impact on mouth-feel [38]. Dziemidowicz *et al*. evaluated the sensory aspects of several co-processed excipients in ODTs formulation which show co-processed excipients that highly composed of sweeteners improved the palatability and acceptability of dosage forms [50].

Investment towards development of excipients is a costly process without a guarantee of return on investment from the sales. To address this challenge, one potential solution is a joint development of excipients with new active pharmaceutical ingredients, which can be incorporated directly into the drug formulation. Additionally, development of multifunctional excipients simplified the number and cost of excipients needed in manufacturing process that are suitable for development of generic drugs. Another potential solution is to develop co-processed excipients for novel dosage forms, particularly when there is limited competition, showing more market freedom [9].

The rapid development of novel dosage forms resulted in the expansion of the pharmaceutical excipients market [27]. Consequently, the development of new type dosage forms is becoming increasingly necessary, demanding specialised excipients with specific functionality to provide optimum productibility and functionality. With all these advantages, the varied combination of excipients and further knowledge of co-processing methods will be an area of concentration for pharmaceutical study from academia and the pharmaceutical industry.

Conclusions

In conclusion, this review show that the development of multifunctional excipients by co-processing two or more existing excipients is a beneficial strategy for producing novel excipients with superior properties. Improvement of physical properties of excipients by co-processing through modification at the sub-particle level further alter the bulk level properties with insignificant changes at the molecular level. Improvement of these functional properties has been proven helpful in enhancing the applicability of excipients, as reported in previous formulation studies of various dosage forms. Moreover, the developed excipients would be a suitable option as low-cost excipients for generic drugs and as the solution in fulfilling the requirement of excipients with specific characteristics for developing novel dosage forms. Consequently, co-processed excipients prospected will still be favourable as research focal points in academics and large-scale application by industries.

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Conflict of interest

The authors declare no conflict of interest.

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