International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 11, Issue 1, 2019

Review Article

A REVIEW ON CO-PROCESSED EXCIPIENTS: CURRENT AND FUTURE TREND OF EXCIPIENT TECHNOLOGY

LIEW KAI BIN[ab*], ANAND GAURAV[a], UTTAM KUMAR MANDAL[c]

[a]Faculty of Pharmaceutical Sciences, UCSI University. No 1, Jalan Menara Gading, UCSI Height, 56000 Cheras, Kuala Lumpur, [b]Faculty of Pharmacy, Cyberjaya University College of Medical Sciences. Persiaran Bestari, 63000 Cyberjaya, Selangor, [c]Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University (MRSPTU), Bathinda, Punjab 151001, India
Email: liewkaia@yahoo.com

Received: 21 Aug 2018 Revised and Accepted: 23 Nov 2018

ABSTRACT

There is no single-component excipient fulfills all the requisite performance to allow an active pharmaceutical ingredient to be formulated into a specific dosage form. Co-processed excipient has received much more attention in the formulation development of various dosage forms, specially for tablet preparation by direct compression method. The objective of this review is to discuss the emergence of co-processed excipients as a current and future trend of excipient technology in pharmaceutical manufacturing. Co-processing is a novel concept of combining two or more excipients that possess specific advantages that cannot be achieved using a physical admixture of the same combination of excipients. This review article discusses the advantages of co-processing, the need of co-processed excipient, general steps in developing co-processed excipient, limitation of co-processed excipient, technologies used in developing co-processing excipients, co-processed excipients in the literature, marketed products and future trends. With advantages offered by the upcoming newer combination of excipients and newer methods of co-processing, co-processed excipients are for sure going to gain attraction both from academia and pharmaceutical industry. Furthermore, it opens the opportunity for development and use of single multifunctional excipient rather than multiple excipients in the formulation.

Keywords: Orally disintegrating tablet, Oral drug delivery, Co-processed excipient, Direct compression

DOI: http://dx.doi.org/10.22159/ijpps.2019v11i1.29265

INTRODUCTION

In the past 10 y, the focus of both academia and pharmaceutical industry has been shifted from developing new active pharmaceutical ingredient (API) to formulation technology [1]. Pharmaceutical excipients have played a major role in that shift. Pharmaceutical excipients are defined as the substances other than the API which has been appropriately evaluated for safety and are intentionally included in a drug delivery system [2]. The International Pharmaceutical Excipients Council (2009) defines excipients as the substances which present in a finished pharmaceutical dosage form other than the active drug substance [3]. Excipient can be classified into four categories generally: single entity excipient, a physical blend of multiple excipients, new chemical entity excipient and co-processed excipient [4].

It is generally agreed by the formulation scientist that there is no single-component excipient fulfills all the requisite performance to allow an active pharmaceutical ingredient to be formulated into a specific dosage form [5]. On the other hand, developing a new chemical entity excipient requires a huge sum of investment [6]. To counter this issue, formulation scientist has introduced a novel concept of co-processing which is combining of two or more excipients that possess significant advantages that cannot be achieved using a physical admixture of the same combination of excipients [7]. A co-processed excipient is a combination of two or more compendial or non-compendial excipients designed to modify their physical properties in a manner not achievable by simple physical mixing, and without significant chemical change [2]. By formulating few excipients into a single composite material with specialized manufacturing method leads to an improvement in functionality of the end product [8]. This has become a newer trend in formulation development [9].

Co-processed excipient has received much more attention in the formulation development of various dosage forms such as a tablet, capsule, powder, cream, ointment, and others [10]. It is different from the physical mixture. Physical mixture is just a simple admixture combining few excipients by short duration shear processing. However, in the case of co-processed excipients, they possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients [11]. Combination of economical excipient with others of optimal quantity of a functional material will produce an integrated product with superior functionality than the simple mixture of components [12]. Co-processing generally does not involve chemical change. The changes in functionality are often contributed by the change in physical properties of the excipient particles [13].

Oral delivery remains the most popular route of drug delivery [14]. It is because the oral drug delivery system has the key advantage of convenient drug administration. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available due to its convenience of self-administration, compactness and simple manufacturing process [15, 16]. Moreover, the drug is found to be more stable in solid dosage form than liquid dosage form [17].

The most common methods to manufacture tablets are wet granulation, dry granulation and direct compression [18]. If the major components of a formulation have already possessed good fluidity and compressibility, granulation would be redundant. Direct compression was reported as one of the most preferred methods due to some advantages such as time-saving, ease of production due to few steps involved, the absence of heat and moisture in the process [19]. In the survey by Shangraw and Damarest (1993), it was shown that direct compression was the most preferred tablet manufacturing method compared to wet granulation and roller compaction. About 41% of the companies indicated that direct compression was the method of choice, and 41.1% indicated that they used both direct compression and wet granulation. Only 1.7% of the respondents indicated that they never used direct compression and 15.5% indicated that the process was not recommended [19].

A further advantage of direct compression is that tablets disintegrate into the primary particles bypassing granular aggregation stage. As a result, the effective surface area increases and dissolution of the drug

become faster [20]. However, the method encounters drawbacks due to lack of suitable excipients for direct compression application. Two major factors of powder characteristic which will critically affect the process of direct compression are compressibility and flowability [21, 22]. The majority of the excipients that are currently available fail to meet the desired set of functionalities. It creates urgency for the development of high functionality excipients [23]. Therefore, the co-processed excipient can play a role here to fill the gap of technology in direct compression.

The aim of this article was to perform a literature review on co-processed excipient and compile as well as discussing the co-processed excipients available in the market and in literature. A detail literature review was conducted by searching keywords such as: a co-processed excipient, orally disintegrating tablet, oral drug delivery, tablet, direct compression, formulation, solid dosage form and powder. The search was done in the search engines including Science Direct, Science and Technology of Advanced Materials, PLOS ONE, Directory of Open Access Journals, CiteSeer and Google Scholar.

Advantages of co-processing

Improved compressibility

Compressibility is an important factor of consideration in tablet development. Ideally, a compacted tablet is formed once the compression force is removed (6). However, all the conventional tablet excipients lack this plastic property. Majority of the co-processed adjuvants overcome this limitation. Flores et al. (2000) reported that the compressibility of Ludipress®, a co-processed adjuvant, is superior than the physical mixtures of their constituent excipients [24, 25].

Better dilution potential

Dilution potential is defined as the ability of the excipient to retain its compressibility even when diluted with another low compressibility material. API and many inactive excipients have poor compressibility. On the other hand, a co-processed excipient with high dilution potential is desirous so that the compressibility properties of the mixture of powder blend can be maintained even when diluted with other excipients [26]. Cellactose® is shown to have a higher dilution potential than the physical mixture of its constituent excipients [27].

Reduced lubricant sensitivity

Generally, hydrophobic lubricant provides a negative impact on the compression behavior of powder blend. Plasticity contributes brittle characteristic to an excipient. The presence of a large degree of brittle character in a co-processed excipient provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network [6].

Ease of production

Co-processed excipient simplifies the tablet formulation and development steps. Tablet formulation normally consists of weighing of active ingredient and various excipients followed by mixing, granulation, drying, sieving, and compression. Weighing of each ingredient might be time-consuming, and it may incur error in the process. Use of co-processed excipient might simplify the production process and reduces the rate of error [28].

Improved flow properties

The co-processed excipient is reported to have better flow properties compared to its individual constituent or physical mixture by controlling the particle size distribution [29]. Good flowability is desired especially in case of high-speed rotary tablet machine [6]. The co-processing excipients play an important role in improving flow property of the powder mass ready for compression. A study showed that the co-processed Cellactose® has better flow than cellulose and lactose due to the spray drying technique used which resulted in particles of spherical shape and even surfaces [30].

Fast disintegration

Fast disintegration is compendial and formulation requirement for immediate release and orally disintegrating dosage form [31]. Co-processed adjuvants, by virtue of their high solubility, swelling and wicking property, provide rapid disintegration to the developed formulation.

Stability

The co-processed excipient should be stable physically and chemically [6]. The ingredients used should be inert and not interact with the API.

Cost saving

The manufacturer uses a single excipient with multiple functional properties, thereby reducing the number of excipients used and labor cost involved in their processing other than direct compression method. Use of co-processed adjuvants simplifies manufacturing process which leads to time and cost saving.

Need of co-processed excipients

A list of available co-processed excipients is provided in table 1. However, they are not sufficient considering the diverse need of the pharmaceutical industries, specially for preparation of ODT tablets. There are only a few excipients are suitable for direct compression application. Most of the excipients having drawbacks such as lack of compressibility, poor flowability, lack of cohesion properties or lubrication [32]. As a result, a blend of few ingredients is required to achieve satisfactory condition prior to direct compression [33]. Moreover, the advance in tableting machinery has resulted in high-speed tablet machine with short duel times. Operation of this machine requires excipients with good compressibility flow property [4].

The role of co-processing comes into the picture by interacting two or more excipients at the sub-particle level, aimed at providing a synergy of functionality improvements, as well as masking the undesirable properties of the individual excipients [2]. The advancement and maturation of co-processing technology explore the possibility to produce tailor-made "designer excipients" to cater to various specific needs required for formulation development [32].

General steps in developing co-processed excipients

In order to design a new co-processed excipient which meets the functionality requirement of a specific application, few steps are important to take into consideration.

a. Identification of the group of excipients to be co-processed

A good co-processed excipient should look into the balance between plasticity and brittleness of a material [34]. Combination of plastic and brittle material nullifies storage of undesirable elastic energy during the compression. This will produce a product with a small amount of stress relaxation and a reduced tendency of capping and lamination thereby optimum tableting performance [35]. The combination of excipient chosen should complement each other and provide synergistic effect to achieve the desirable characteristics [6].

b. Assessing the particle size

Particle size will affect the compressibility and flowability of the end product. If the participating excipients have variation in initial particle sizes, the focus should be given to produce the final co-processed adjuvant with uniform particle size.

c. Selecting a suitable technique to co-process various excipient

There are many methods which can be used for co-processing such as wet granulation, melt granulation, freeze drying, spray drying, hot melt extrusion [36-39]. A comprehensive detail has been provided later in this review.

d. Optimizing the process and the proportion of each excipient

This can contribute to functionality variations in the end product. Various optimization techniques and experimental designs with sound statistical analysis can be employed to obtain a final product with desired functionalities.

Limitation of co-processed excipient

Although co-processed excipient shows a list of promising benefits, however, there are few drawbacks in using of co-processed

adjuvants. Co-processed adjuvant is available as pre-mixed at a fixed ratio of an individual constituent. The user has no freedom to alternate the ratio of the excipient [40]. Moreover, co-processed adjuvant lacks the official acceptance in pharmacopeia [41]. For this reason, a co-processed adjuvant is not accepted by the pharmaceutical industry unless it exhibits significant advantages in the tablet compaction when compared to the physical mixtures of the excipients [2].

Technologies used in the manufacturing of co-processed excipients roller compaction

Roller compaction uses the principle of dry granulation for particle bonding. This method is useful for ingredients which are sensitive to moisture and heat. The powder blend is mixed uniformly and compressed between counter-rotating rollers to form a ribbon of compacted material that is then milled into granules of appropriate particle size [42-44].

Wet granulation

Wet granulation is a conventional and simple method for co-processed adjuvant production. Fluid bed granulators and high-shear mixers are two commonly used equipment used for the same. In fluid bed granulation, the powder mix is subjected to fluidization by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed in the opposite direction to the air flow on the powder bed. The solid particles are mixed with the liquid droplets and hit the bed which results in adhesion and eventually the formation of granules. Partial drying by the fluidizing air occurs continuously during granulation [45-47].

In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel. The binder solution is sprayed from the top. Development of large agglomerates is prevented by high shear force. With the new single-pot technology, drying occurs in the same system. The granules formed are understandably denser than those obtained in fluid bed granulation [48].

Hot melt extrusion

Hot melt extrusion uses heat with a temperature greater than 80 °C. This method is not suitable for thermo labile materials. The excipients are melted and then pressurized through the die and solidify into a variety of shapes. The solvent is not required in the process as the molten polymer can function as a thermal binder [49].

Spray drying

Spray drying generally involves five steps: Concentration of feedstock, atomization, droplet-air contact, droplet drying and separation and collection [50-51]. The technique transforms a feed which might be a solution, suspension or dispersion into dried particulate form by spraying it into a hot drying medium. The particle-particle bonding of excipients occurs during the process. The increased droplet surface area and high temperature cause the formation of spherical shape particles with improved flowability and suitable direct compression application such as Starlac®.

Roller drying

A roller dryer is used to dry the homogeneous solution or dispersion containing the pre-blended excipients. Meggelaars *et al.* (1996) applied this technique to co-process lactose with sorbitol and lactitol [52]. The temperature used was sufficiently high to obtain an end product that consists principally of β-lactose in crystalline form.

Co-transformation

Co-transformation technique involves the application of heat or solvent effect to "open-up" (swelling) the particle of one excipient. The other excipients are incorporated into the "opened-up" structure of the aforementioned excipient. The augmented excipient strengthens the functionality of the end product [53, 54].

Milling

A roller mill, ball bill, bead mill, millstone mill, jet mill or a hammer mill can be used to perform milling or dry grinding. The excipients are premixed and passed through a high-speed milling machine. During the process of milling, the particles come in contact with each other and form bonds when they are subjected to force to mill or pass through the screen. Rao *et al.* (2012) applied this technique to co-process cross-linked polyvinylpyrrolidone and calcium silicate [55].

Melt granulation

The blend of excipients are mixed with a meltable binder (normally at solid state below 80˚C). The mixture is subjected to heat above the melting point of the binder with continuous blending in order to break the mass into agglomerates. The cooled agglomerates are finally screened to obtain granules with desired size [56-57].

Solvent evaporation

Solvent evaporation takes place in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent which is immiscible with the liquid manufacturing vehicle, followed by dissolving or dispersing the core excipient in the coating solution. Agitation force is applied to achieve the desired encapsulation size. Heat is used to evaporate the solvent [4].

Co-processed excipient in the literature

Microcrystalline cellulose (MCC) and calcium carbonate

Mehra *et al.* (1986) patented a co-processed excipient of microcrystalline cellulose and calcium carbonate. The co-processed excipient was used to produce a directly compressed vitamin tablet. The invention was economical and exhibited low lubricant sensitivity [58].

Lactose, polyvinylpyrrolidone (PVP) and crospovidone

Lang (1991) reported a blend of lactose, PVP and crospovidone which was produced through spray drying, spray granulation or wet granulation method. The novel direct tableting auxiliaries exhibited good flow, good compressibility under low pressure, excellent disintegration properties coupled with great hardness and low abrasion [59].

β-lactose and sorbitol

Meggelaars *et al.* (1996) prepared a homogeneous mass consisting of a dried solution of high β-lactose content with sorbitol ranges from 1-15% % w/w. Roller drying technique was used in the drying process. The excipient can be used to prepare tablet with exclusive hardness [52].

Cornstarch and polyvinylpyrrolidone

Menon *et al.* (1996) described a co-processed excipient consisting of cornstarch and polyvinylpyrrolidone produced using fluid bed spray granulation method. The invention is free-flowing and exhibits good compressibility [60].

Colloidal silicon dioxide and MCC

Sherwood *et al.* (1996) patented a novel MCC-colloidal silicon dioxide excipient that was found to be free flowing, possess excellent disintegration properties and have improved compressibility relative to normal "off the shelf" commercially available MCC [61].

Guar gum and MCC

Ratnaraj and Reilly (1997) produced a co-processed excipient for the chewable tablet by thoroughly mixing an aqueous dispersion of MCC and guar gum under high shear conditions at room temperature. The homogenous dispersion was then spray dried to an aggregate powder having substantially spheroidal-shaped particles. The excipient has improved compressibility and mouth feel. It reduces tooth packing [62].

Directly compressible sucrose

The invention contains 95% sucrose and 5% of maltodextrin. This sugar-based excipient is free-flowing, compressible and has a pleasant taste and mouthfeel which can be helpful in masking the bitter taste of API [63].

MCC and methylcellulose

Augello and Vladyka (1999) invented a co-processed excipient by wet granulating MCC and methylcellulose. The compositions were then subjected to spheronizing into spheres having a smooth uniform surface. The end product serves as a coating polymer which provides complete taste masking of a bitter drug such as ibuprofen while having no adverse impact on the bioavailability of the drug [64].

MCC and sodium alginate

The invention is a wet granulation binder type excipient by Augello and Reier (1999). A uniform aqueous slurry of MCC and sodium alginate was formed firstly, followed by drying the slurry to granular particular [65].

Alfalfa, MCC and calcium carbonate

Ibrahim and Saraiya (2001) developed a co-processed excipient comprised of alfalfa root, MCC and calcium carbonate. Spray dried procedure was used in the development process. The said product was applied to formulate vitamin and nutritional supplements [66].

MCC and maltodextrin

Buliga *et al.* (2002) blended MCC and maltodextrin and sprayed dried the dispersion. The invention was reported to mix with carboxymethyl cellulose to produce a dry blend that can be used in food and cosmetic application as stabilizer [67].

Rice starch and MCC

Limwong *et al.* (2004) invented a co-processed excipient comprising of rice starch and MCC. Composite particles of rice starch and MCC were fabricated by spray-drying technique to be used as a directly compressible excipient. The compressibility was greater than commercial spray-dried rice starch (Eratab), coprocessed lactose and microcrystalline cellulose (Cellactose), and agglomerated lactose (Tablettose), but, lower than microcrystalline cellulose (Vivapur 101) [36].

Calcium phosphate and fatty acid wax

Cucula *et al.* (2006) produced a co-processed excipient containing calcium phosphate and fatty acid wax (glyceryl behenate or glyceryl palmitostearate) using melt granulation method. Co-processing of calcium phosphate with fatty acid wax overcomes the abrasiveness and capping issues normally associated with calcium phosphate. It was applied to formulate venlafaxine HCL modified release tablet, and venlafaxine besylate extended-release tablet [68].

Sorbitol and mannitol

Norman *et al.* (2006) reported a blend of sorbitol and mannitol prepared by dissolving mannitol powder and sorbitol powder into a solution. The solution was then dried in an air stream and forming a composition that completely dissolves in the oral cavity within 60 seconds. The invention is suitable for orally disintegrating tablet application [69].

Crospovidone and sodium starch glycolate

Gohel *et al.* (2007) developed the co-processed excipient through wet granulation and tray drying technique. Blend of crospovidone and sodium starch glycolate was added to isopropyl alcohol for wet granulation. The wet mass was sieved and dried in a tray dryer. The end product exhibited good flow property, compaction and disintegration property. The invention was applied as a superdisintegrant in the formulation of cefiximetri hydrate and ibuprofen tablet [37].

Copolymer of vinylpyrrolidone (VP) and vinyl acetate (VA) and MCC

Halder *et al.* (2007) developed a co-processed adjuvant containing a copolymer of vinylpyrrolidone, vinyl acetate and MCC. This synergistic binder composition was applied to produce tablets with exclusive hardness and acceptable friability. It is suitable to be used in tablet formulation containing poorly compressible drug [70].

MCC and mannitol

Slurry of MCC and mannitol were sprayed dried to spherical particulate. The composition had an improved compatibility profile, lubricant sensitivity, and ejection profile compared to the physical mixture and individual component [71].

Mannitol and calcium silicate

A co-processed excipient which is suitable for orally disintegrating tablet application was developed by Gandhi *et al.* (2009). Mannitol was dispersed in water followed by dispersing calcium silicate in the solution. The mixture was spray dried to granules. The tablet produced by compression of the excipient disintegrated in less than 60 seconds [72].

Crospovidone and croscarmellose sodium

Nagendrakumar *et al.* (2009) blended croscarmellose sodium and crospovidone in ethanol. The mixture was stirred until most of the ethanol evaporated. The wet coherent mass was sieved and dried in a hot air oven. The invention serves as a co-processed superdisintegrant. It was applied to formulate granisetron fast dissolving tablet [73].

Mannitol and cellulose

Patel SS and Patel NM (2007) prepared a co-processed excipient of mannitol and cellulose for dispersible tablet application. The end product was prepared using the freeze-thawing method and was claimed to have an improvement in flowability, compatibility and dissolution rate of a model drug [9].

Povidone and glyceryl behenate

Ayyappan *et al.* (2010) developed a co-processed adjuvant comprising povidone and glyceryl behenate which was claimed to function as binder and lubricant with good flow and compressibility. The co-processed excipient was applied to manufacture tramadol HCl control release tablet and it provided a drug release profile comparable with Zydol SR [74].

Microcrystalline and spray dried lactose

Dey *et al.* (2010) produced co-processed excipient of various ratio combination of microcrystalline cellulose, spray dried lactose and pearlitol. The study concluded that co-processed excipient of microcrystalline and spray dried lactose at 90:10 % w/w was the optimum formulation which showed good compressibility and fast disintegration. The product was applied to formulate paracetamol orally disintegrating tablet [75].

Sodium carbonate and polyethylene glycol

The invention is a pH modifier developed by Davar *et al.* (2010) using a fluid bed spray granulation method. Polyethylene glycol protects sodium carbonate from moisture which results in caking. The said invention was applied in the non-effervescent pharmaceutical composition of zolpidem and scopolamine [76].

Starch and magnesium silicate

Adnan *et al.* (2011) co-processed starch with magnesium silicate. Starch was suspended in a suspension first followed by addition of magnesium silicate. The suspension was then filtered, washed and dried. The dried product was used to prepare tablets with high mechanical strength, short disintegration time and low lubricant sensitivity [77].

Lactose, MCC and cornstarch

Akram *et al.* (2011) developed co-processed micro-granules of lactose monohydrate, MCC and cornstarch by wet granulation. The finished product was claimed to have the strong binding ability, fast disintegration time and improved flow property [78].

α-chitin and mannitol

Al Omari *et al.* (2011) published research on the development of α-chitin and mannitol co-processed excipient by fluid bed spray granulation method. The invention was applied in the orally

disintegrating tablet to contribute to exclusive hardness, low friability, low ejection force while retaining rapid disintegration properties [79].

Dibasic calcium phosphate, HPMC and crospovidone

Deorkar *et al.* (2011) formulated an invention by co-processing dibasic calcium phosphate as a brittle material component, HPMC as binder and crospovidone as a disintegrant. The invention showed an increased flowability, API loading, and blendability and higher compatibility [80].

MCC and HPMC

Deorkar *et al.* (2011) prepared a co-processed excipient by spray dry granulating an aqueous slurry comprised of the microcrystalline cellulose and HPMC. Then invention has enhanced flowability, high compatibility, and increased API loading and blendability as compared to the individual components [80].

Maize starch and acacia

Olowosulu *et al.* (2011) developed co-processed excipient of maize and acacia by co-drying or a well dispersed aqueous mixture of the two. The drying was performed on a water bath system at 50°C and 80°C for 15 min with constant stirring respectively to compare the effect of partial and fully gelatinization. The fully gelatinized form showed good flowability but poor crushing strength. In contrast, the tablets produced by partially gelatinized form showed good crushing strength and friability profile [81].

Calcium phosphate and MCC

Thoorens *et al.* (2011) invented a calcium phosphate and MCC co-processed excipient by mixing the aqueous slurries of microcrystalline cellulose and calcium phosphate, followed by drying such slurries to produce particulate products. The end product exhibited improved compatibility, as compared to dry physical blends of the same components [82].

Polyox WSR-301 and HPMC K4M

The co-processed excipient was reported by Gangurde and Amin (2013) using roller compaction method. Polyox WSR-301 and HPMC K4M powder samples were forced between two counter-rotating rolls and screened through 60 mesh sieve. The obtained fine powder was further recycled to get granules of uniform size. The finished product was applied to produce metformin HCl sustained release tablet [83].

Dicalcium phosphate and carboxymethylcellulose sodium

Ambore *et al.* (2014) studied on various ratio combination of dicalcium phosphate and carboxymethylcellulose co-processed using co-precipitation method. The study concluded that the flow property of the co-processed excipient improves significantly compared to the physical mixture. The excipient had good dilution potential and was used to produce a tablet with poorly compressible drugs such as paracetamol and ibuprofen [29].

Dicalcium phosphate and carboxymethylcellulose sodium

The invention was developed by Ambore *et al.* (2014) using co-precipitation technique. Carboxymethylcellulose was dispersed in water to allow it to swell. Dicalcium phosphate was dispersed in another portion of water. The two portions of dispersion were mixed and dried in tray dried. The invention was reported to have better flowability and dilution potential [29].

Chitosan and Eudragit S-100

Pawar *et al.* (2014) prepared a co-processed excipient of chitosan and Eudragit S-100 using the solvent evaporation method. The co-processed excipient was applied to produce venlafaxine HCl sustained release tablet via direct compression [84].

Lentinus tuber regium base co-processed excipient

Ugoeze and Nkoro (2015) developed a co-processed excipient by mixing Lentinus tuber regium, sodium bicarbonate, tartaric acid and citric acid using solvent evaporation method. The end product appears as a compactable, tasteless, off-white powder without distinct odor. The flow property, compressibility, and dilution potential were improved [12].

Marketed products

There are many marketed products of co-processed excipients available. The marketed products are presented in table 1.

Table 1: Products of co-processed excipients which are available in the market

Trade name	Excipients	Manufacturer	Added advantage	Reference
Ludipress	Lactose, kallidon 30, kallidon CL	BASF	Low degree of hydroscopicity, good flowability, tablet hardness independent of machine speed	85
Cellactose	Lactose and cellulose	Meggle	High compressibility, good mouth feel, better tableting at low cost	86
Dipac	Sucrose and dextrin	Penwest Pharm	Directly compressible grade	87
Prosolv	Microcrystalline cellulose and silicon dioxide	Penwest Pharmaceuticals	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability	88
Avicel ce-15	Microcrystalline cellulose and guar gum	FMC Corp.	Less grittiness and minimal chalkiness	89
Formaxx	Calcium carbonate and sorbitol	Merck	High compressibility, excellent taste masking, free flow, superior content uniformity, controlled particle size distribution	90
Microcelac	Microcrystalline cellulose and lactose	Meggle	Capable of formulating high dose, small tablets with poorly flowable active ingredients	91
Starlac	Lactose and maize starch	Meggle	Good flowability due to spray drying, the acceptable crushing force due to lactose content and rapid disintegration depending on	56

			starch.	
Pharmatose DCL 40	β-lactose and anhydrous lactitol	DFE Pharma	Spherical shape particle with good flowability, good binding property and not hygroscopic	92
Starch 1500	Amylose, amylopectin, and starch	Colorcon	It is a directly compressible, free-flowing, USP grade of partially hydrolyzed cornstarch. The tablets produced disintegrates very fast	93
Pearlitol SD	Granulated mannitol	Roquette	Suitable for chewable tablet application with good mouthfeel and palatability	73
Advantose FS-95	Fructose and starch	SPI Polyols	Good mouthfeel and fast disintegration property. Suitable for nutraceuticals and chewable vitamin applications	90
Finlac DC	Directly compressible lactitol	Cultor Food Science	Direct compression grade. Good mouthfeel and fast disintegration property. Suitable for nutraceuticals and chewable vitamin applications	94
Plasdone S-630	Vinyl acetate and vinyl pyrolidone	ISP	Good roller compaction binder, improved hardness and better drug dissolution profile	24
Lycatab C	Pregelatinized starch	Roquette	Suitable for moisture sensitive API.	95
Copovidone	Kollidon VA 64 and plasdone S630	Ashland	Excellent flow properties and dry binder	24
Ludiflash	Mannitol, crospovidone and polyvinyl acetate	BASF	Suitable for high-speed tableting, low friability, and good flowability	41
Orocell 200 and Orocell 400	Spheronized mannitol	Pharmatrans Sanaq	Filler-binder with high dilution potential and good disintegrating property	41
Cel-O-Cal	Microcrystalline cellulose and calcium sulphate	FMC Biopolymer	Directly compressible binder	41
Tablettose	Spray dried lactose (agglomerated form)	Meggle	Good flowability and direct compressible	96
Xylitab	Xylitol and sodium carboxymethylcellulose	Danisco	Directly compressible and good palatability	97
StarCap 1500	Maize starch and pregel starch	Colorcon	Tablet disintegration and dissolution independent of pH	98
Vitacel VE-650	Microcrystalline cellulose and calcium carbonate	FMC Biopolymer	Suitable for direct compression and encapsulation	97
LustreClear	Microcrystalline cellulose and carrageenan	FMC Biopolymer	Efficient Tablet coating with short hydration time prior to coating and the first drying time	2
Pharmaburst	Carbohydrate system, made from compendia ingredients	SPI Pharma	High compatibility, high loading in, small tablets, smooth mouth, feel, rapid, disintegration	99
Effersoda	Sodium bicarbonate and sodium carbonate	SPI Pharma	Improve the stability of the Effervescent product	2
Sorbcel M	Mannitol, polyethylene glycol, polyvinylpyrrolidone, citric acid and sodium bicarbonate	Blanver	Effervescent excipients, Homogeneous and stable mix of excipients that dissolves completely and rapidly, resulting in a clear solution free of insoluble residues	2
Sorbcel E	Sorbitol, mannitol, polyvinylpyrrolidone, citric acid and sodium bicarbonate	Blanver	Effervescent excipients, A homogeneous and stable mix of excipients that dissolves completely and rapidly, resulting in a clear solution free of	2

			insoluble residues	
Fujicalin	DCP anhydrous	Fuji Chemicals	Directly compressible, exceptional high flow and rapid disintegration	100
Neusilin	Amorphous magnesium aluminometasilicate	Fuji Chemicals	Improve flow, anti-caking, improve Compressibility and to make solid dispersion	101
F-Melt	Carbohydrate, disintegrant and DCP	Fuji Chemicals	Directly Compressible, oral Disintegrating time less than 30 seconds, highly flowable with minimum or no sticking/capping	51
Sepitrap 80	Polysorbate 80	Seppic	Improves the bioavailability of APIs with low solubility. It can be used in direct compression processes	95
Sepitrap 4000	Ethoxylated hydrogenated castor oil	Seppic	Improves the bioavailability of APIs with low solubility. It can be used in direct compression processes	95
Tap-400	Processed tartaric acid pellet	Pharmatrans	As an acidic core for drug Delivery technologies	2

Future trend

Traditional inert excipients with lack of desired functionalities have drawn the attention of pharmaceutical formulator in developing new co-processed adjuvants. The recent developments in the field of excipients, advancement in high-speed manufacturing machinery and novel co-processing techniques have further added driving force for the growth of this field. An exploration of solid-state properties of excipients and its impact on functionality is further going to fuel this trend. Moreover, increase cost in developing new chemical entity and an increasing preference for the direct compaction process create a significant opportunity for the development of high-functionality co-processed excipients. It is predicted that the development of tailor-made designed excipients complying with safety, performance, and regulatory issues is a current and future trend in excipient technology [95]. With advantages offered by the upcoming newer combination of excipients and newer methods of co-processing, co-processed excipients are for sure going to gain attraction both from academia and pharmaceutical industry [102]. Furthermore, it opens the opportunity for development and use of single multifunctional excipients rather than multiple excipients in formulation [103].

CONCLUSION

The co-processed excipients play a pivotal role in formulating stable, result oriented drug delivery system with an improved physical, chemical and mechanical properties [104]. Furthermore, co-processed excipients solve the issues of precompression parameters, compressibility, palatability, disintegration, dissolution, and sticking which conventional individual excipients might have. Co-processed excipient is a promising tool in pharmaceutical excipient development [105]. The existing co-processed adjuvants cannot fulfill all the functionalities required for preparation of various novel formulations. Cost is another factor that incurs increased the price of the final product. So, there is enough scope of development of new co-processed excipients to meet the demand of pharmaceutical industries. It is expected that advanced research in academia and pharmaceutical industry will surely bridge this gap in the near future.

ACKNOWLEDGMENT

The authors would like to acknowledge Pioneered Scientist Innovation Fund (PSIF grant, grant no: Proj-In-FPS-007) for sponsoring the research project. We thank Faculty of Pharmaceutical Science, UCSI University for providing facilities.

CONFLICT OF INTERESTS

The authors report no declaration of interest

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