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CO-PROCESSED EXCIPIENTS, THEIR CHARACTERISTICS AND ACTUAL RANGE

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The article covers a new generation of excipients such as multifunctional co-processed excipients, manufactured by coprocessing. The article shows the results of the search for co-processed excipients presented in the modern pharmaceutical market, as well as scientific studies reflecting the main aspects of their application.

Keywords: co-processed excipients, coprocessing, orally disintegrated tablets, chewing tablets, solid dosage forms

Current trends in the development of solid dosage forms (DF) are reduced to the choice of technologies that ensure the consistency of the quality of the medicine. Simplification of the production process eliminates the need to validate additional production stages, thus eliminating the risk of their impact on quality. Co-processed excipients are increasingly widely being used which are a mixture of two or more excipients of different functional classes, produced by co-processing, most often by spray drying technology, in which there is no change in the chemical structure of the initial components and the formation of new substances [1,2]. The development and implementation of co-processed excipients will simultaneously solve a number of problems related to both the medicine quality assurance and the logistics of the production process. The main prerequisites for the development of co-processed excipients were the increasing tendency for developers to choose the direct compression technology (DC) as the cheapest and easiest to perform, and the lack of a "universal" excipient, which would have all the necessary properties to produce the dosage form with the characteristics required by the direct compression technology. Co-processed excipients are a separate generation of excipients produced

using well-known and proven technologies already widely used in the production of dosage forms of excipients, such as spray drying, melt granulation, wet granulation, fluidized bed granulation, etc.

In addition, due to the growing interest in the opportunities that open up with the use of 2D and 3D technologies in the development of solid dosage forms, co-processed excipients can become excipients for tablets produced by three-dimensional printing [3].

LACTOSE-BASED CO-PROCESSED EXCIPIENTS

Lactose is the most common diluent in solid dosage forms due to its low cost, availability, physicochemical stability, and good solubility. Lactose exists in several forms, which differ in physical and processing characteristics. For example, β-lactose is found only in anhydrous form, whereas α-lactose can be obtained both in anhydrous form and as a monohydrate.

Crystalline α-lactose monohydrate (α-LM) has a poor binding capacity compared to lactose produced by spray drying, or β-lactose, which is characterized by plastic deformation due to the predominance of the amorphous fraction. In addition, the use of α-LM as a diluent in direct compression technology is limited by its poor flowability and compressibility, which is due to the insufficient cohesive ability of the particles. The use of spray drying technology contributed to the improvement of processing characteristics, as a result of which Tablettose® and Pharmatose® DCL 15 (DFE Pharma, Germany) were produced. However, the ability to press these products is limited by a certain limit, above which the tablet has insufficient crushing strength.

Low *dilution potential* (dilution capacity) is also a limitation in the use of α-LM in direct compression technology. Dilution capacity is the ability of a diluent to retain its compressibility properties when mixed with another component with poor compressibility. The concept of dilution capacity is applied to diluents for direct compression and is estimated by increasing the value of the area parameter under the curve (AUC) of the tablet strength dependence on the compression pressure. The method for evaluating the dilution capacity is proposed by *Minchom & Armstrong* (1987) and consists in mixing the test filler with a gradually increasing amount of the second component with poor compressibility and following measuring the area under the AUC curve of the tablet strength dependence on the compression pressure. The curve allows us to calculate the dilution capacity index (DCI) for further use as a comparison value for two fillers [4].

The solution to the problem of poor compressibility was found in the combination of α-LM with microcrystalline cellulose (MCC), povidone (PVP) or starch, but this did not significantly affect the flowability, which became a prerequisite for the creation of co-processed excipients produced by the method of co-processing.

Ludipress® (BASF, Germany) is white free-flowing lactose granules (93%), covered with a film of povidone (3.5%) (Kollidon® 30) and crospovidone (Kollidon® CL). There is also Ludipress® LCE without disintegrant (Table 3). Ludipress® is odorless and tasteless and is used in the development of tablets and gelatin capsules. The process of such a product also allowed to reduce the hygroscopicity of lactose and to ensure the independence of the strength of the tablets from the pressing speed.

It is noted that, despite the presence of a disintegrant, tablets with Ludipress® disintegrate longer than tablets based on α-LM, anhydrous β-lactose, lactose produced by spray drying, or Tablettose®, which is explained by increase of PVP in proportion to increase of Ludipress®. Ludipress® proves to be a more effective disintegrant (4–8%) compared to croscarmellose sodium and povidone, which provides high release of API (active pharmaceutical ingredient) of class II

according to the Biopharmaceutical classification system – up to 99% [5].

During the disintegration test, tablets with Ludipress® produced at compression pressure of 100 MPa showed a minimum value of the disintegration time, which did not change with increase in the compression pressure, which was not observed in tablets with Cellactose® (>20min.). It is noted that the use of Ludipress® as a diluent ensures the weight variation during continuous tablet forming. It was found that the strength of tablets increases in proportion to the compression pressure up to 300 MPa and does not depend on their diameter, thickness and shape [6,7].

Cellactose® 80 (Meggle Pharma, Germany) due to the uniformity of the fraction composition has good flowability and was developed for the direct compression process. Cellactose® has greater dilution capacity compared to a physical mixture of similar composition and less hygroscopicity due to the inclusion of MCC. The plasticity of microcrystalline cellulose (MCC) particles helps to improve the particle adhesion and compressibility of lactose monohydrate [8]. It is suitable for tablets with a high dosage and has a good adhesive ability, which is important when applying coatings [9].

MicroceLac® 100 (Meggle Pharma, Germany) is a co-processed excipient in which the embedding of MCC (25%) in α-LM (75%) is carried out by spray drying process. MicroceLac® 100 is characterized by a lower tendency to delamination compared to a similar physical mixture, and also allows to significantly increase the compressibility of a tablet mixture with API with unsatisfactory processing characteristics [10].

CombiLac® (Meggle Pharma, Germany) is another multifunctional diluent based on α-LM (70%), MCC (20%) and native corn starch (10%). Tablets made of CombiLac® show significantly higher values of crushing strength compared to MicroceLac® 100. When pressing, CombiLac® and MicroceLac® 100 exhibit predominantly elastic deformation. The disadvantage of both co-processed excipients is poor microbiological stability, confirmed by experiment, *Eline Byl et al.* [11].

Starlac® (Meggle Pharma, Germany) is a bifunctional co-processed excipient prepared from α-LM (85%) and corn starch (15%). The compressibility of lactose is increased by starch fibers, which provide a binding and disintegrating action when swollen in water. Starlac® is recommended for development of tablets with rapid release of API, since the distinctive feature of Starlac® – based dosage form is the independence of the disintegration time from the strength of the tablets and the absence of the influence of the amount of antifriction substance on the compressibility. In comparison with the rest of the above mentioned co-processed excipienты, Meggle Pharma is the least suitable for high-dose formulations [12].

A comparison of the suitability of Meggle Pharma co-processed diluents for direct compression process by the SeDeM diagram method allows us to conclude that Starlac® and MicroceLac® 100 are significantly inferior in compressibility to Cellactose® 80. However, due to the fibers of the MCC, Cellactose® 80 is more hygroscopic compared to Starlac® and MicroceLac® 100 [13]. Starlac®, MicroceLac® 100, and Cellactose® 80 are used as diluents in the development of microcapsule tablets for oral use [14].

RetaLac® (Meggle Pharma, Germany) is a co-processed diluent based on α-LM (50%) and hypromellose of type K (viscosity 4000 MPa *s) (50%) for development of the dosage form with modified pH-independent release of API. The co-processed excipient is produced by fluidized bed process. Due to the inclusion of α-LM, the wettability of hypromellose is improved and the disintegration of the tablet is accelerated.

Anhydrous lactose has a higher flowability value and is suitable for direct compression, but this value is lower than optimal one due to the high content of the dust fraction. In addition, at high humidity, there is a noticeable increase in

the weight of the tablet. Co-processed excipient **Pharmatose® DC DCL 40** (DFE Pharma, Germany), consisting of anhydrous lactose (95%) and anhydrous lactitol (5%), was developed. Among all the lactose-based composite diluents, Pharmatose® DC DCL 40 has the best binding and diluting properties in comparison with the other co-processed excipients and is characterized by low hygroscopity.

Among the monosaccharides, fructose and sucrose are also distinguished as a diluent. The main limitations of fructose as a diluent are poor compressibility and formation of too strong granules when moistened with water. Improvement in the processing characteristics of fructose was found in the preparation of **Advantose® FS 95** (SPI Pharma, France) by joint spray drying with starch (5%). In addition, Advantose® FS 95 is superior in taste to sucrose (20% sweeter) and is approved for use in patients with diabetes. Advantose® FS 95 is used as a diluent for tablets from microcapsules for oral administration [14].

Di-Pac® (Domino Spec. Ingredients, USA) is a diluent for direct compression based on sucrose 97% and dextrin 3%, which has high porosity, due to which a uniform distribution of API in the volume is ensured. Porous Di-Pac® co-crystals are produced by cooling a supersaturated solution with continuous stirring. Excellent solubility allows the use of Di-Pac® for the accelerated release dosage form. Low hygroscopicity (up to 1%) is also called the advantage of Di-Pac®.

MCC-BASED CO-PROCESSED EXCIPIENTS

MCC has the greatest dilution capacity among the diluents used in the solid dosage form process. The disadvantage of the MCC is decrease in compressibility when interacting with water. The loss of the functional properties of excipients as a result of interaction with water in the foreign scientific literature is called as "quasihornification", which is literally translated as "the effect of quasihornification", and co-processing allows us to reduce this effect. An example of improving the compressibility of the MCC can be its co-processing with silicon dioxide. Thus, the **Prosolv®** line of diluents (JRS Pharma, Germany) was developed.

The Prosolv® line is represented by three types of co-processed excipients: Prosolv® SMCC 50, Prosolv® SMCC 90 and Prosolv® SMCC HD 90. The difference between the latter two excipients is connected with the different bulk density and the ability to maintain the uniformity of the mass of the tablets during the compression process. The introduction of silicon dioxide provides a barrier to moisture, which is sorbed by particles at a humidity value of up to 52%. At higher humidity values (≥72%), the absorbed moisture reduces the deformability of the particles and can lead to increase in the disintegration time of the tablet. There is evidence of decrease in the absorption of API of derivatives of amines (tacrine hydrochloride) from aqueous solutions of MCC. The disadvantage of Prosolv® SMCC HD 90 is its high sensitivity to anti-friction substances. Comparative study of the mutual effect of Prosolv® 90 HD / Prosolv® 50 and low-compressible API (such as ibuprofen (50 microns) and acetaminophen) on the compressibility of the binary mixture showed that the ratio of the API and diluent particle sizes affects the functionality of the diluent in case of the increase of API loading (up to 60%) [15].

FMC Health Nutrition (USA) is a manufacturer of a multifunctional Avicel® diluent based on MCC, prepared by the method of joint spray drying (Table. 1) [16].

SUGARS AND POLYOLS -BASED CO-PROCESSED EXCIPIENTS

Polyols are widely used in the development of oral dispersible (ODT) and chewable tablets as diluents and sweeteners, since they have

suitable organoleptic properties and quickly dissolve when interacting with the dissolution medium [17]. However, as mono diluents, they do not have the processing properties necessary for the direct compression process.

Thus, the process of sorbitol compression is complicated by high hygroscopicity, which is the reason for poor compressibility and caking as well as affects the properties of the finished tablets (crushing strength, dissolution kinetics, bioavailability of API).

Compressol™ SM (SPI Pharma, France) is a mixture of mannitol and sorbitol for direct compression, high compressibility of which is provided by sorbitol, and almost 300 times decrease in sensitivity to moisture is provided by mannitol. Therefore, Compressol™ SM is recommended primarily for formulations with moisture-sensitive and poorly pressed API. Tablets with Compressol™ SM show good disintegration. SPI Pharma also produces spray-dried co-processed excipients for ODT **PharmaBurst® 500**

Table 1

THE RESULTS OF THE COMPARISON OF PROPERTIES OF DIFFERENT TYPES OF AVICEL® (FMC HEALTH NUTRITION, USA)

Trademark	Composition	Features highlighted by the manufacturer	Properties [16]
Avicel® CE-15	MCC (85%), guar gum (15%)	Development of chewable tablets (suitable organoleptic properties, creamy structure, without graininess)	The particles accumulate a negative charge on the surface, but are more easily powdered. Compared to the other types, the composition shows a lower value of the disintegration time and crushing strength of the tablets as well as greater hygroscopicity. Due to guar gum, it has characteristic organoleptic properties. It is not recommended to use as a diluent with pH-sensitive API.
Avicel® HFE 102	Avicel PH 102, mannitol (10%)	Improved flowability due to the inclusion of mannitol	It is characterized by better flowability due to large symmetrical sphere-like particles; moderate hygroscopicity, worse exposed to powdering due to the constantly changing charge on the surface of the particles. Tablets have a higher value of crushing strength and a longer disintegration time.
Avicel® DG	MCC (75%), dicalcium phosphate (25%)	It is recommended for compaction process. Possibility of repeated compression without loss of compressibility properties	The lowest value of flowability due to asymmetric and small particles with a stable charge; has a low hygroscopicity. It shows a relatively good ability to powder and the crushing strength of the tablets, while the tablets quickly disintegrate. It is suitable for wet granulation technology in formulations with moisture-sensitive API.

tablets based on D-mannitol (85%), silicon dioxide (<10%), sorbitol (<10%) and crospovidone (5%).

Ludiflash (BASF, Germany) consists of 90% mannitol, 5% crospovidone (Kollidon CL-SF) and 5% polyvinyl acetate (Kollicoat SR30D). Co-processed excipient is characterized by low sensitivity to moisture and reduces the probability of delamination of the tablet mixture with API. Ludiflash® is used in the development of ODT tablets [18,19], and also as component that accelerates the disintegration of tablets with API having poor solubility in water [20].

Parteck® ODT (Merck KGaA, Germany) is a co-processed excipient based on joint spray-dried D-mannitol (95%) with croscarmellose sodium (5%) for development of ODT tablets. Mannitol is in its most stable polymorphic modification i.e. the β-crystalline form, which has a melting point of 155–156°C [21,22].

A comparison of the two diluents on the example of metformin tablets showed that at a pressure value of 5.0 and 7.5 kN and 40–50% concentration of Parteck® ODT in the tablet, they delaminate in contrast to tablets based on Ludiflash® [23].

F-MELT® (Fuji Chemical Industry Co., Ltd, Japan) is a coprocessor diluent consisting of mannitol, xylitol, MCC, crospovidone disintegrant and one of the inorganic substances such as magnesium aluminosilicate (Neusilin ®) or dicalcium phosphate (Fujicalin ®). There are three types of F-MELT: M, C, and F1, depending on the functional features (Table. 3) [24]. A study by Karolina Dziemidowicz et al. demonstrated that patients prefer the tablets with F-MELT® diluent of type C in terms of taste sensations, although there is no significant difference between types C and M [25].

SmartEx™ (Shin-Etsu Chemical, Japan) is a three-component co-processed excipient based on mannitol, hypromellose with a low degree of substitution as a disintegrant and polyvinyl alcohol as a binder. Two types of SmartEx™, differing in particle sizes, have been developed (Table. 2) [26].

A study by *Karolina Dziemidowicz et al.*, which aimed to identify a co-processed diluent for ODT tablets with the best organoleptic profile, identified SmartEx™ QD-100 as the most preferred among patients in the following sequence: SmartEx™ QD-100 > F-MELT C > F-MELT M > MicroceLac > Ludiflash [25].

Xylitab® (Danisco A/S, Denmark) co-processed excipient is xylitol (98%), treated with sodium carboxymethylcellulose (2%), can be used in direct compression process in the development of tableted dosage forms for various applications, especially chewable tablets due to the cooling effect [26].

CO-PROCESSED EXCIPIENTS WITH INTEGRATED LUBRICANTS

The study of the effect of a lubricant such as magnesium stearate on the processing parameters of tablets and API release from a tablet [27],

Table 2

CHARACTERISTICS OF SMARTEX™ (SHIN-ETSU CHEMICAL, JAPAN)

Type	The range of the spread of the particle size, microns	Average particle size, microns	Recommendations
QD-50	45–75	51.6	To reduce the desintegration time
QD-100	85–125	85.3	To increase the compressibility

Table 3

A SUMMARY TABLE OF CO-PROCESSED EXCIPIENTS OF THE VARIOUS GROUPS

Trade name	Manufacturer	Composition	
		Brittle component	Plastic component
Sugar based			
Ludipress®	BASF, Germany	Lactose 93,5%	Povidone (Kollidon 30) 3,5%, Crospovidone (Kollidon CL) 3%
Ludipress® LCE		Lactose 96,5%	Povidone (Kollidon 30) 3,5%
Cellactose® 80	Meggle Pharma, Germany	α-Lactose 75%	MCC 25%
Microcelac® 100	Meggle Pharma, Germany	Lactose 75%	MCC 25%
CombiLac®	Meggle Pharma, Germany	α-Lactose 70%	MCC 20%, Native corn starch 10%
Starlac®	Meggle Pharma, Germany	α-Lactose 85%	Corn starch 15%
RetaLac®	Meggle Pharma, Germany	α-LM 50%	Hypromellose, Type K (50%)
Pharmatose® DCL 40	DFE Pharma, Germany	Lactose ahydrous 95%	Lactitol anhydrous 5%
Disintequik ODT	Kerry Ingredients & Flavours, USA	Lactose	Desintegrant (?)
Disintequik MCC 25	Kerry Ingredients & Flavours, USA	α-LM	MCC
Di-Pac®	Domino Spec. Ingredients, USA	Saccharose 97% Dextrine 3%	–
Advantose® FS 95	SPI Pharma, France	Fructose 90%	Starch 5%
MCC based			
Prosolv® SMCC 50/90/HD 90	JRS Pharma, Germany	Silicon dioxide 2%,	MCC 98%
Prosolv® ODT		Silicon dioxide, Fructose	MCC, mannitol, crospovidone
Prosolv® EastTab		Silicon dioxide	MCC, Sodium starch glycolate, Sodium stearyl fumarate

End of the table 3

Trade name	Manufacturer	Composition	
		Brittle component	Plastic component
Avicel CE-15	FMC Corporation, USA	–	MCC 85%, guar gum 15%
Avicel® HFE 102		–	Avicel PH 102 90%, mannitol 10%
Avicel® DG		Calcium hydrogen phosphate 25%	MCC 75%
Polyol based			
CompressolTM SM	SPI Pharma, France	–	Mannitol, sorbitol
Ludiflash®	BASF, Germany	–	Mannitol 90% Polyvinylacetate 5% Crospovidone 5%
Parteck® ODT	Merck KGaA, Germany	–	Mannitol 95% Cross-carmellose sodium 5%
F-MELT® type C	Fuji Chemical Industry Co., Ltd, Japan	Fujicalin® 2–9%	D- mannitol 55–70% Xylitol 2–9% MCC 10–25% Crospovidone 5–13%
F-MELT® type M		Neusilin® 2–9%	
F-MELT® type F1		Fujicalin®	Waxy Rice Starch MCC
SmartEx™ QD-50/100	Shin-Etsu Chemical, Japan	–	Mannitol Low-substituted hypromellose
PharmaBurst™500	SPI Pharma, France	Silicon dioxide <10%	Mannitol 85% Sorbitol <10% Crospovidone 5%
Xylitab® 100/200	Danisco A/S, Denmark	–	Xylitol 98% Sodium carboxylmethylcellulose 2%
With integrated lubricants			
LubriTose™ MCC	Kerry Ingredients & Flavours, USA	LM 98%	Glyceryl monostearate 2%
LubriTose™ AM			Glyceryl monostearate 4%

as well as its toxicological properties (for example, irritating effects on the epithelium of the gastrointestinal tract) excites especial interest [28,29]. Manufacturers are faced with the urgent task of finding alternatives to lubricants that are not inferior in functionality to the classic derivatives of stearic acid.

The **LubriTose™** line of fillers (Kerry Ingredients & Flavors, USA) was developed to simplify the production process by introducing a lubricant into one of the most commonly used fillers such as lactose anhydrous (96%), MCC (98%) or mannitol (96%). Glyceryl monostearate (2% – LubriTose™ MCC; LubriTose™ AM – 4%) is used as a lubricant. Thus, comparative studies of the co-processed diluent LubriTose™ MCC and a mixture of Vuvapur® 12 glyceryl monostearate showed a lower value of the friction force energy and the maximum plastic deformation of the co-processed diluent, which indicates the elimination of the supermixing effect [30,31]. However, there is evidence that LubriTose™ MCC is inferior in the time of disintegration of ibuprofen tablets in comparison with magnesium stearate, while tablets based on the LubriTose™ MCC co-processed excipient and a physical mixture of MCC with glyceryl monostearate did not show a significant difference in the time of disintegration [32].

OTHER CO-PROCESSED EXCIPIENTS

The range of co-processed excipients for direct compression process is constantly expanding, and pharmaceutical manufacturing companies offer new multifunctional platforms and delivery systems.

Advantol™ 300 (SPI Pharma, USA) Sof™elt delivery system is a ready-made powder mixture for direct compression, prepared by the method of co-processing, which has suitable organoleptic properties and quickly disintegrates upon contact with aqueous medium. This system is suitable for development of chewable tablets for pharmaceutical and nutraceutical applications. Advantol™ 300 is a relatively new product on the pharmaceutical market and its composition and process are not disclosed by the manufacturer.

Pharmasperse® 416 (SPI Pharma, USA) is a platform for oral dispersed powders (ODP) which is an alternative to tablets and is available in the form of sachets or stick bags. Pharmasperse® 416 has a refreshing taste with a cooling effect, which allows it to be used to mask the taste of API. The diluent has low hygroscopicity and uniform fractional composition, due to which it has an excellent flowability characteristic.

New co-processed excipients **Disintequik™ ODT** and **Disintequik™ MCC 25** produced by Kerry Ingredients & Flavours (USA) based on LM and disintegrant have been developed for use as diluents in ODT tablets.

REGULATORY STATUS OF CO-PROCESSED EXCIPIENTS IN USP/NF

Co-processed excipients are also subject to the registration process. The main parameter by which the quality and safety of co-processed excipients is checked is confirmation of the absence of chemical interaction between the components of the co-processed excipient. In this case, the composite diluent does not require additional toxicological studies and can be recognized as safe and approved for pharmaceutical use – GRAS (generally recognized as safe). To assign the GRAS status, it is also necessary that all components of the co-processed excipient have the GRAS status.

For each new co-processed excipient, a monograph is required; since the process for their production involves physical interaction, analytical methods for evaluating the quality of the initial components are not quite suitable for quality control of a co-processed diluent. To confirm the fact that a co-processed excipient is composite, at least

one analytical qualitative experiment is required, the results of which distinguish it from a physical mixture with the similar qualitative and quantitative composition.

The classifier of functional assignments of excipients in the Eurasian Economic Union does not contain any references to co-processed excipient. In December 2015, a draft monograph "Co-processed Excipients" was included into the European Pharmacopoeia (Ph. Eur.) 27.4, which states that the components of the co-processed excipient must meet the requirements of the monographs for each specific substance. In 2016, an updated draft of the USP Guideline for Submitting Requests for Revision to *USP-NF,* Submission Guideline for Excipients, was submitted for review for inclusion into the USP, which notes the key parameters for which excipients can be classified as co-processed, as well as the requirements for them. The Guideline fundamentally distinguishes a co-processed excipient from a physical mixture and focuses on the need for analytical tests aimed at confirming the absence of covalent bond formation during their production and storage.

IPEC, International Council of Manufacturers, Distributors and Consumers of Active Pharmaceutical Ingredients (Excipients) of the United States and Europe have jointly developed and published the first edition of the Co – Processed Excipient Guide (2017). The Guide allow manufacturers and consumers of co-processed excipients to come to an understanding in resolving the issues related to providing the latter with information on the safety of co-processed excipient to provide data to regulatory authorities when registering medicines included in co-processed excipients. Each co-processed excipient is accompanied by a master file that meets the requirements of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), so, as a rule, there are no difficulties in the process of registering a medicine containing a co-processed excipient.

As analytical methods for the determination of co-processed excipient, the Guide suggests taking into account the methods recommended by the IPEC Excipient Qualification Guide (2008) and the USP monograph "Monograph Submission Guidelines for Excipients", including testing for such indicators as "Mass loss during drying", "Residual organic solvents", "Elemental impurities" (ICH Q3D), particle shape and size distribution. When choosing or developing a method for defining the co-processed excipient, you should choose those that allow you to detect covalent bonds, so it is most rational to recommend several different analytical methods to ensure the accuracy of the results.

CONCLUSIONS

Engineering of new multifunctional co-processed excipients is a promising direction in the field of solid dosage form development due to the demand for direct compression process. The undeniable advantages of using the co-processed excipients, such as the simplification of the technological production flow diagram, the reduction of the stages at which the quality control and validation are required, as well as the time of the production cycle itself, allow the co-processed excipients to firmly occupy their pharmaceutical business segment.

An obvious limitation of the use of co-processed excipients is the fixed proportion of components in the composition of the co-processed excipient, which can significantly reduce the number of APIs and their dosages suitable for inclusion into a pharmaceutical composition based on the co-processed excipient. It should also be noted that it is necessary to develop more specific principles of the methodology and clarify the requirements for them to confirm the stability of the co-processed excipient structure as part of the medicine and during storage.

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