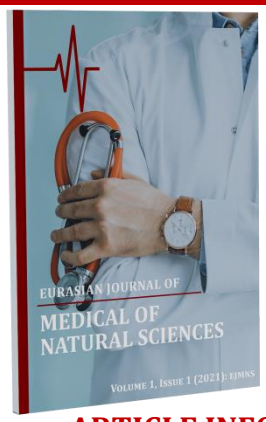
EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
UIF = 8.3 | SJIF = 7.921 www.in-academy.uz



MODERN EXCIPIENTS IN THE PRODUCTION OF TABLETS

Dusmetova Zhamila Raufovna
Rakhimova Gulnora
Maksudova Firuza Khurshidovna
Azimova Nargiza Abbaskhanovna
Rakhimova Oigul

https://doi.org/10.5281/zenodo.11028998

ARTICLE INFO

Received: 12th April 2024
Accepted: 19th April 2024
Online: 22th April 2024

KEYWORDS

tablet, disintegrants, antifriction agents, disintegrants, fillers, colorants, disintegration, gastrointestinal tract, sodium carboxymethylcellulose, acid alginic, twins, fluidity, dosing accuracy, binding substances, lactose, physicochemical properties, pharmacokinetics.

ABSTRACT

In modern conditions, the competitiveness of drugs is determined not only by the direction of their action, relevance, but also by the level of quality, quality-price ratio. In creating conditions for the production of competitive solid dosage forms, in particular tablets, a scientifically based selection of high-quality excipients is essential. In the development and improvement of the production of modern solid dosage forms, the leading role is played by high-molecular compounds, which make it possible to create drugs with predictable biopharmaceutical and technological parameters. In domestic pharmaceutical production, a new generation of high-molecular auxiliary substances produced by foreign companies is increasingly being introduced.

Introduction. A wide range of new synthetic polymers that create conditions for the controlled release of medicinal substances from the dosage form makes it possible to create optimal conditions for the implementation of the activity of medicinal substances of various chemical structures and directions of action. The introduction of superdisintegrators into practice makes it possible to significantly improve the bioavailability of poorly soluble drugs and maintain a high level of quality, hardness, and strength of tablets. The use of new, universal high-molecular auxiliary substances that combine several functions creates the prerequisites for optimizing the technological process. Thus, expanding the range of excipients with a new generation of high molecular weight compounds creates new opportunities for improving the tableting process and tablet quality.

In the production of the vast majority of tablets, excipients are used. Their importance in the production of tablets is very great. Therefore, in recent years, the number of studies aimed at finding new natural and synthetic compounds that can be used as excipients has sharply increased. Excipients, depending on their purpose, are divided into the following groups: 1) Diluents or fillers; 2) Loosening; 3) Gluing; 4) Sliding; 5) Lubricants or anti-adhesive substances; 6) Coloring; 7) Prolonging the action; 8) Corrigents and others. Diluents include: lactose, sucrose, glucose, mannitol, glycine, calcium carbonate, calcium sulfate dihydrate,

calcium sulfate hemihydrate, calcium hydrogen phosphate, dextrin, sodium chloride, dried sodium sulfate, kaolin, basic magnesium carbonate [1-5].

The most commonly used filler lactose. Disintegrants are divided into 3 groups.

1. Substances that ensure the destruction of tablets in a liquid medium as a result of chemical interaction with the formation of carbon dioxide. These can be mixtures of: a) tartaric or citric acid with sodium bicarbonate; b) citric acid with calcium carbonate.

2. Substances that have the ability to swell in a liquid medium. These are amylopectin, ultraamylopectin, bentonites, alginic acid and its salts, sodium carboxymethylcellulose. Pectins are part of pectin substances - high molecular carbohydrates of plant origin. The skeleton of pectic substances is pectic acid, consisting of D-galacturonic acid. Pectins are products of varying degrees of methylation of pectic acid, soluble in water and form dense gels in the presence of sugar or organic acids. Alginic acid is a polysaccharide isolated from algae, consisting of D-mannuric acid (MW 50-200 thousand). Soluble in hot water, forms gels. Sodium alginate (algin) is soluble in cold water, artificial silk is obtained from it, and is used in the food industry as a stabilizer.

3. Substances that increase the wettability of the components included in the tablets. These are 0.2% twins. If there are more than 1% Tweens in a tablet, then the strength of the tablets is lost. This group includes various types of starch, which reduce the strength of interparticle contacts and cause the formation of a porous structure, facilitating faster penetration of digestive juices into its mass. Starch acts as a capillary-forming substance [5-8].

Adhesives are divided into 2 groups: 1. Humidifiers - water, ethyl and methyl alcohol, chloroform, acetone, carbon tetrachloride, isopropanol. During drying of the granulate, the humectants completely evaporate. 2. The actual solutions of adhesives: starch solutions from 2-5% to 10-15%, solutions of alginic acid, sodium alginate, pectins, proteins (gelatin, casein, zein), sugar syrup, etc. This also includes cellulose derivatives: 1 -2% aqueous solution of methylcellulose, 4-8% alcohol solution of ethylcellulose, carboxymethylcellulose, sodium salt of carboxymethylcellulose, aqueous-alcohol solution of gelatin. A solution of polyvinyl alcohol and a 10% aqueous solution of polyvinylpyrrolidone are also used. Cellulose derivatives: methylcellulose - cellulose methyl ether of varying degrees of substitution. The maximum content of methoxy groups is 45.6%. Methylcellulose containing 14-35% methoxyl groups is soluble in cold water [3].

Ethylcellulose is cellulose ethyl ether. Carboxymethylcellulose is an ester of cellulose and glycolic acid. Polyvinyl alcohol is obtained from vinyl alcohol CH2 =CHOH, which is not isolated in its pure form. Polyvinylpyrrolidone - white powder, soluble in water, M.m. 2-200 thousand. It is also used as a blood substitute, detoxification solution (hemodesis 6%) and as a prolonger of the action of penicillin and novocaine [8-13]. Gliding substances are divided into 3 groups: 1. Granulates that improve flowability (starch, talc, polyethylene oxide, aerosil, skim milk powder); 2. Anti-adhesive substances reduce the adhesion of powders to the matrix and punches (stearic acid and its Mg, Ca, Al salts, paraffin, ceresin, silicone lubricants); 3. Mixed action glidants: siliconized talc, mixtures of Ca stearate and talc, gleytol, ligroin gel of A1 stearate, mixture of talc with cetyl alcohol. Hydrophobic lubricants (talc, stearic acid, magnesium and calcium stearates) significantly slow down the disintegration of tablets, while hydrophilic lubricants (sodium oleate, sodium lauryl sulfate, etc.) do not have such an effect.

Hydrophilic lubricants belonging to the group of surfactants (polyethylene glycol esters with high molecular weight fatty acids and polyethylene glycol esters with high molecular weight saturated alcohols) in some cases can reduce the disintegration time of tablets. To prevent the tablet mass from sticking to the punches and the walls of the matrix hole, Teflon (polytetrafluoroethylene) films are applied to the latter [13-18].

Excipients also include dyes, which have recently begun to be widely used in the production of tablets. Speaking about the use of dyes in the production of tablets, one cannot fail to mention the great danger of brightly colored tablets for children. Based on this, the issue of coloring tablets, especially those containing toxic and potent substances, should be decided with great caution. All existing dyes can be divided into 3 groups: paints, pigments and specks. Dyes include: chlorophyll (green), echrot (red), naphthol red amaranth, quinoline yellow, lactoflavin, brilliant black, carotene, carotenoids, gelborang, indigo, tartrazine, eosin for mercuric chloride.

The domestic pharmaceutical market is currently characterized by high saturation and a large share of analogues and generics. Under these conditions competitiveness medicinal drug determined Not only his relevance, demand, but also the level of quality, as well as the ratio of quality and price. All options quality medicinal facilities to one degree or another depend on the auxiliary tools used substances That's why their optimal Increasing attention is being paid to selection [18-20].

The composition of the excipients used is significantly influences Also on conditions carrying out technological process, structural and mechanical indicators and consumer properties of the finished product , and therefore - on its cost. Currently there is a large assortment (approx. 6000 titles) auxiliary substances used in the production of solid dosage forms, in particular tablets [21-22]. Depending on the physicochemical properties of the active (medicinal) substances, the method of their preparation, recommended dosages and a number of other factors, apply auxiliary substances, playing different roles: fillers (thinners), disintegrants (disintegrants), antifriction agents (sliding agents, lubricating) funds, proofreaders taste , regulators of the dynamics of release of the active substances, dyes And row others. However clear separation auxiliary substances By their roles V medicinal form No. One And That or a substance, depending on the method of its application, can be used for different purposes [1–3].

As fillers (used to obtain tablets With dosage current substances to 10 mg) potato starch is most often used, input inside granulates, A Also sucrose, lactose, glucose, magnesium carbonate, calcium carbonate, urea, mannitol and others [23].

Disintegrants are added to tablets to improve their disintegration in the gastrointestinal tract. tract, What necessary For release and subsequent suction current substances. Various substances are used as leavening agents. chemical nature: potato starch used at the stage of powdering the tablet mass, as well as methylcellulose, sodium carboxymethylcellulose, acid alginic And her sodium salts, amylopectin (improves disintegration behind check swelling), twins (improve wettability particles), a mixture of citric or tartaric acid with sodium hydrocarbonate (destroys tablet V one environment behind check gas formation). Disintegrants are usually selected individually, So How one And That or substance can improve the solubility of some drugs and hinder the solubility of others [25-28].

In order to improve fluidity, increase the accuracy of dosing of powdered material, ensure necessary technological properties granulates And tablets are used connecting substances, humectants: water, ethanol, sugar syrup various concentrations, 5–10 % starch paste solution, 5–20 % solutions polyvinylpyrrolidone, 1–10 % solutions of gelatin and gum arabic, 1–2% aqueous solutions of methylcellulose and hydroxypropylmethylcellulose, 4–8% alcohol solutions of ethylcellulose, alginic acid gels, alginates and others. Their composition and quantitative ratio are selected individually in each specific case [28-31].

Anti-friction (reducing friction) substances increase flowability granulates, prevent sticking of the tablet mass to the working parts, facilitate pushing out pills from matrices. Their subdivide on 3 subgroups: I - sliding (starch, talc, kaolin, aerosil, skim milk powder, polyethylene oxide-4000); II - lubricants (stearic acid and its salts, vaseline oil, Tween, polyethylene oxide-400, silicon carbons); III — substances that prevent adhesion (talc, starch, stearic acid, its calcium and sodium salts) [32].

Dyes and pigments in the production of solid dosage forms, including tablets, are used With purpose improvements commodity type of finished product, and also as markers indicating on special properties given drug: its belonging to a certain pharmacotherapeutic group (hypnotics, narcotic drugs); high level toxicity (poisonous) And other. From domestic pharmaceutical dyes are used indigo carmine (blue); tropeolin 0 (yellow); acid red 2C (red); dioxide titanium (white) And other. B Kharkov New coloring materials (cerulesum, ruberosum, flavarosum, orangezoum), which can be used in the production of coated tablets. The possibility of using new natural dyes, V in particular, chlorophyll And carotenoids. Behind abroad For staining solid Dosage dosage forms use coloring substances classified as pigments [24-25, 33]. The important role of excipients in realizing the potential activity of the active substance medicinal shapes, A Also V technological process determine a number of requirements placed on them. They must have necessary chemical purity, stability of physical parameters, pharmacological indifference. Together they should ensure optimality technological process, have sufficient production base, affordable cost [34].

A significant number of currently used time domestic pharmaceutical included in the State Register of Medicines by the excipient industry; These substances have pharmacopoeial articles regulating their quality.

When developing tablet dosage forms and selecting excipients, it is of great importance It has usage accumulated experience their application and experimental study. An analysis of the data presented in recent publications indicates that many substances considered previously indifferent, Not quite correspond to this characteristic. Thus, it was found that lactose, which has long been considered one of the most indifferent diluents, can actively influence the pharmacokinetics and activity of some drugs. substances. B result complexation she reduces therapeutic Effect isoniazid [35-36]. The presence of lactose increases the rate of testosterone absorption, as well as the release phenobarbital from solid dosed medicinal forms Lactose, A Also sucrose And glucose, significantly reduce suction caffeine from gastrointestinal tract. Basic substances such as magnesium carbonate and sodium salt of carboxymethylcellulose reduce the stability of alkaloid salts in tablets [37].

Many medicinal substances in the presence of certain auxiliary components become unstable And undergo chemical changes [37-39]. A.I. Tentsova found that resorption

fluoroacyzine from tablets, containing lactose and sucrose, on 15 – 20 % below, how from tablets, containing crystalline cellulose And calcium disubstituted phosphate [17]. Talc in large quantities can call irritation mucous membrane shell stomach and the formation of granulomas [18].

Thus, auxiliary components are not a passive component of the dosage form. Drugs, containing one And that or active substance, but different composition of excipients, may differ in effectiveness and other characteristics. Of particular importance is scientifically based selection auxiliary substances For creation oral dosage forms of drugs, the effect of which can only be carried out in certain, specially created with the help of excipients , conditions. This, V in particular, applies To drugs whose active substance is destroyed in acidic environment stomach, A Also medicinal forms of prolonged actions, requiring definite , strictly dosed exit active started from medicinal shapes, And a number of others. B medicinal forms such sort of auxiliary substances are actually an integral part of the drug. Variety of chemical structure, physicochemical properties, focus actions And pharmacokinetic behavior medicinal substances as well as production, economic and commercial tasks determine necessity constant search for new compounds for the development and improvement of dosage forms [19, 20].

In the production of tablets, various high-molecular compounds, both natural and synthetic, are widely used as excipients. IN latest years along with With them new ones have also begun to be used. Row foreign firms produce V the present time new polymer materials, which allow us to predict certain technological And biopharmaceutical parameters of medicinal products . Copolymers of acrylic and methacrylic acids are used abroad as materials for tablet shells. A special place among them is occupied by substances produced by the company “Rohm Pharma” (Germany), under the general name “Eudragit”. They are organic solutions or aqueous variances synthetic copolymers methacrylic acid and its esters. Depending on the ratios carboxyl And ethereal groups, these polymers dissolve at various values pH. Along with With sensitivity To pH environment They can vary And speed dissolution. Their used for receiving shells tablets, allowing regulate the place of release or the speed of release of the active substance from the dosage form, or simultaneously the place and speed of release. Yes, Eudragit E is weak basis, used For creating coatings that dissolve in the stomach. Substances of the Eudragit family L ensure the release of the active substance in various parts of the intestine: Eudragit L100 – 55 and Eudragit L30-D-55 - in the 12-ring intestine; Eudragit L- 100— in region thin section to the ileum. Eudragit S 100 is soluble in the pH range of 6.0 to 7.5, which is typical for the area near the colon. To create oral forms with pH-independent release of the active substances are used representatives families RL, RS and NE . Wide range modifications of copolymers produced company, allows create optimal conditions For implementation activity of substances of different chemical structures and directions of action [21–27]. Row synthetic polymers, creating conditions for the controlled release of active substances from solid dosage dosage forms are also produced by BASF under the general name “Collicote”. Among them are substances for creation shells, sustainable or soluble in the acidic environment of gastric juice, as well as coatings that provide prolonged or, conversely, immediate release current substances from medicinal forms. Some from

polymers (Collicote VAC) can be used both to create a tablet shell and as a matrix for the controlled release of the active substance [28–30].

A number of products have been created based on polyvinylpyrrolidone (PVP) products, found application V modern pharmaceutical technologies. Firm BASF release big range modifications PVP various appointments under general brand "Kollidon". IN about production solid dosed medicinal the most widely used forms are Plasdone K, Polyplasdone And Plasdone S630 Plasone K is used as a viscosity modifier and solubilizer, as well as How binder means For granules And release regulator of the active substance. Plasdone S630 provides opportunity direct pressing and dry granulation, Maybe Also be used V quality plasticizer For film coatings [31-34]. A mixture of lactose monohydrate and two polymers, Kollidona thirty And Kollidona Cl (branded name “Ludipress”), which is a granulate of a certain size, is used as a universal aid. Ludipress can be used And How filler, And How binder means, A Also With purpose improvements flowability of the technological material and disintegration of tablets [29-30].

Important place V technologies solid dosed medicinal forms occupy various modifications And derivatives cellulose. They are used at different stages of the technological process and, depending on the characteristics of the structure and method of application, can play a different role [35]. We had 4 dyes approved for use in production: indigo carmine, tartrazine, acid red 2C, tropeolin 0 and 3 colored materials - ruberosum, cerulesum, flavarosum. In the USA, aluminum specks are used as dyes. In total, 120 types of dyes are used in the world. In the USA and England - 60-80 titles. WHO has approved the use of the 10 most harmless dyes. In the practice of drug therapy, it is sometimes necessary that the tablet drug introduced into the body does not disintegrate for a long time. For this purpose, the prescription includes compounds that provide prolongation of action when taken. The action of these compounds is opposite to the action of disintegrants. Substances that provide prolongation include: aluminum hydroxide gel, polyvinylpyrrolidone, sodium proteinate, polyoxyethylene sorbitan, mercaptogelatin, glycerol monostearate. High molecular weight fatty acids and their mixtures, hydrogenated cottonseed oil, etc. are also used. In the literature of recent years, there have been reports that it is possible to prolong drugs using ion exchange resins [10-14]. Since 1962 Microcrystalline cellulose (MCC) is used in the production of tablets. They receive it by partial hydrolysis cotton cellulose acid hydrochloric. Existing MCC brands vary By degrees polymerization; the most commonly used brands are MCC “Avicel” and “Vivapur” With size particles 50–160 μm. MCC described in British, European pharmacopoeias And V US Pharmacopoeia. One of the advantages of MCC is its low cost. MCC is insoluble in water, acids, and organic solvents. MCC crystallites are used How dry binding means, How diluent, as well as to improve the disintegration of tablets. Near authors shown opportunity use crystallites And V quality framework-forming substance for water-soluble and water-insoluble substances [36, 37]. MCC is compatible with various drugs substances especially moisture sensitive. As a disintegrant, MCC is effective in a mixture with starch and its modification products. Despite the relative chemical inertness, MCC at certain conditions Maybe interact with the components of the dosage form. Thus, when it is ground with acetylsalicylic acid in a vibrating mill, “grafted complexes” are formed [38].

How it is known primary mechanism release of soluble active ingredients from the tablet is diffusion through layer gel, A insoluble - superficial erosion (destruction) pills. The universal material for the production of soluble matrix tablets is the inert pharmaceutical filler hydroxypropylmethylcellulose. (HPMC), described in everyone specialized reference books. Wide range molecular weights this connections allows easily provide gelation with a given value of relative viscosity. For creation enteric dosage forms often use acetylphthalylcellulose (APC), representing yourself mixed ether cellulose, acetic and phthalic acids [12]. Depending on the content of phthalyl and acetyl groups and a number of other conditions, it has a different speed dissolution. B pharmaceutical AFC containing phthalyls is most often used in production groups thirty – 38 %, acetyl groups – 18-23% [14]. Used as gastric soluble coatings polymers, containing amino groups: diethylaminocellulose , benzylaminocellulose And others [15]. To apply water-soluble coatings to the surface of tablets, solutions of polyvinylpyrrolidone are used, methylcellulose, sodium and aluminum salts of carboxymethylcellulose, hydroxypropyl methylcellulose, polyethylene oxide, shellac and other materials [18]. Sodium carboxymethylcellulose (Na CMC) is used as an emulsifying, gelling and binding agent. Used as a tablet shell, this polymer can also play the role of a release regulator of the active (drug) substance [19].

As is known, of the two existing tableting methods, the direct compression method is economically significantly more profitable [3]. However, this method can only be used if the material being tableted has certain properties: good flowability, compressibility, good adhesive interaction between medicinal and auxiliary substances, and a number of others. In addition, this method may not always ensure uniform dosing medicinal substances And necessary qualities of tablets. Only 10 % of medicinal powders that have the necessary properties can be subjected to direct pressing. B quality of substances providing the possibility of direct pressing, apply MCC, polyvinylpyrrolidone V combination With lactose, modified polyvinylpyrrolidone (plasdon S630), modified starch, aerosil, calcium diphosphate, maltodextrose and others [28, 31].

The majority of medicinal powders require special preparation before tabletting. For this purpose, a method for producing tablets is used, which involves granulating the powder before tableting. The task of granulation is the formation of particles of certain sizes, shapes, structures And physical properties. Granulation allows you to adjust the technological properties of powders, provides more uniform distribution active component, more accurate mass tablets and the dose of the active substance, reduces the influence of temperature and humidity on the quality of tablets [24-25].

Currently, several granulation methods are used; the most widely used method wet granulation - multi-stage process, usually including about 8 stages. This method is most effective in most cases, however very labor intensive. Use new materials as binding components allows to reduce the number of stages. Thus, use as a filler And binder means specially processed starch (drying by centrifugation) “Prejel”, “Prejel PA5 PH”, issued company AVEBE (Holland), allows reduce stages soaking And cooking starch gel and, therefore, reduce costs. In some cases it is possible to use methods dry granulation, What significantly reduces costs. The possibility of dry granulation provides, V in particular,

application PVP, modified PVP (plasdon S 630), as well as MCC, Na CMC and some other binding agents [28, 31].

Binding components used when wet granulation, unequally influence on race fall rate tablets. Many from them worsen disintegration. A comparative study revealed significant differences By degrees influence on disintegration of tablets between ethylcellulose, polyvinylpyrrolidone, carboxymethylcellulose, methylcellulose And gelatin. Not worsens, a, on the contrary, dextrin (primogran) improves the disintegration of tablets W from AVEBE), which can simultaneously play the role of a filler and a binder. A study of the effect of various modifications of Na CMC on the disintegration of tablets showed that a product with a high degree of polymerization has the best properties in this regard And small number carboxyl groups [12, 33]. With purpose acceleration disintegration tablets various leavening agents are used (listed above, in at the beginning articles). Along with With them V latest years More and more wide apply so called “super disintegrants”. They are cross-linked polymers obtained from potato starch, carboxymethylcellulose or polyvinylpyrrolidone. Swelling in water, but not dissolving, they create conditions for accelerated disintegration of the tablet. Compared to conventional disintegrators, They act significantly stronger, are used in smaller quantities. As practice has shown, introduction super disintegrators significantly increases tablet disintegration and release little soluble V water medicinal substances, in particular flavonoids. Using too much superdisintegrant to increase solubility hydrophobic medicinal substances, Maybe drive To the opposite result [12, 20].

Superdisintegrants can be used either independently or in various combinations with each other. or With ordinary baking powder, V depending on specific conditions (degree of hydrophobicity of the active ingredient, pH of the environment, etc.) [33, 35].

special role play superdisintegrants V those cases when there is a need to use a lubricant in the technological process - an anti-friction substance added to prevent sticking tablet masses V pressing machine. In these cases, adding sufficient lubricant dose significantly reduces disintegration pills, A application ordinary raising agents V effective doses can significantly reduce the strength (hardness) of the tablet. Use of superdisintegrant allows V tens once speed up disintegration and at the same time maintain the required tablet hardness. At comparative studying superdisintegrants it has been established that a more stable effect is observed at different parties sodium glycolate (modified cross-linked starch), compared with different batches of croscarmellose sodium (cross-linked sodium carboxymethylcellulose) [34-39].In Russia, superdisintegrants produced by AVEBE (Netherlands) are officially registered - sodium starch glycolate (Primogel, HD 42-11282-00) (Netherlands) and croscarmellose sodium (Primelose, HD 42–11281–00). Under general under the name “Primojel” the company produces several modifications of the sodium salt of cross-linked, partially oxidized O-carboxymethylated potato starch. Depending on the content of sodium ions in the molecule (normalized from 2 to 5 %), they are divided, according to Pharmacopoeia USA [38], on 3 type (A, B, C), differing in the degree of viscosity of the gels they form, pH and a number of other properties. Unlike regular starch, Primojel in the optimal dose does not reduce the hardness of the tablet. As practice has shown, the use of superdisintegrators of the Primojel family is advisable, in particular, in the production of formulations with a high content of active substances [20].

An important point is the fact that AVEBE produces Also row connecting substances, fillers And others auxiliary materials that combine well with superdisintegrants. Thus, good results were obtained in the “Disintegration” and “Dissolution” tests of metronidazole and acetaminophen tablets, which included such excipients produced by this company, How Prejel (Prejel starch — filler), potato starch native (baking powder, registered V RF — HD 42-10337-99, AVEBE company, Netherlands), Primogel (sodium salt modified cross-linked starch - superdisintegrant) [38, 39].

Conclusion. Coming on domestic wound foreign companies producing quality traditional auxiliary substances And auxiliary substances new generation, creates conditions for competition between various manufacturers of these products and the opportunity for the consumer to choose the best options for excipients that can provide the required level of quality of drugs and the profitability of their production.

References:

1. Sheskey, PJ, Cook, WG, and Cable, CG, 2017, Handbook of Pharmaceutical Excipients, Pharmaceutical Press, The Royal Phramaceutical Society of Great Britain, p. 138-152; 505-527.
2. GK Bolhuis and ZT Chowhan, “Materials for direct compaction,” Pharmaceutical Powder Compaction Technology (ed. Alderborn G, Nyström C), Marcel Dekker, New York, 2013, pages 419-478.
3. W. Zebrowska and W. Sawicki, “Excipients,” The applied pharmacy (ed. S. Janicki, A. Fiebig, M. Sznitowska), PZWL, Warsaw 2008, pages 652-693.
4. Yu.E. Kirsch, Chemical-pharmaceutical journal, 17(6),7 – 1 1 (2014).
5. Michoel, A., and Rombaut, P., 2022, Comparative evaluation of co-processed lactose and microcrystalline cellulose with their physical mixtures in the formulation of folic acid tablets, Pharm Dev Technol., 7; 79-87.
6. Patent USA 5225206 MKU A 61 K 9/16, 9/54 Sustaned release pranoproten preparation. Fushimi Magurani, et al., no. 192563374.
7. Patent 5492696 USA MKU A01 No. 25/34, 59/20. Control led release microstructures R.P. price, P.E. Schoen, M. Testoff, et al., no. 194563275.
8. Mamatha, B., Srilatha, D., Sivanarayani1, CH, Prasanna KD, and Rao, P.V., 2023, CO-Processed Excipients: An Overview, World J Pharm Res., 6(15); 224-237
9. A.P. Zuev, N.P. Sadchikova, Tyulyaev, Chemical-pharmaceutical journal. , 37 (11), 29–31 (2022).
10.V.M. Lehtola , J.T. Heinamaki , P. Nikupaavo, et al., Drug Dev. and Ind. Pharm. , 21 (12), 1365 – 1375 (2012).
11. Y. Kane, J. Rambaud, H. Maillols, et al., Drug Dev. and Ind. Pharm. , 20 (6), 1021 – 1034 (2018).
12. USP-NF, 2018, The United States Pharmacopeia and the National Formulary, USP 41–NF 36, The United States Pharmacopeial Convention, Rockville, USA p.7011
13.E. A. Hosny, Pharm . Act a Helv., 72 (5), 255 – 261 (2021).
14. N.H. Shah, J. Lazarus, PR Sheth, S.J. Jarowsky, J. Pharma ceut. Sci. , 6 , 611 – 613 (2019).
15.R.Thribert, S. T. P. Pharma Sci , 2 (11), 123 – 128 (2023).

16.MR Laura, M.L. Torre, I. Maggi, S.T.P. Pharma Sci , 4 (11), 265–269 (2022).
17.G.K. Bolhuis, Eur. J. Pharm. Sci , 2 (5), 63– 69 (2022).
18.C. R. Chen, Chem. Pharm. Bull. , No. 46, 478 – 481 (2023).
19.TA Miller, P. Yorc, Int. J. Pharm. , 41.1–19 (2024).
20.G.K. Bolhuis, A.J. Smallenbroek, and C.F. Lerk, J. Farm. Sci , 70 , 1328 (2021).
21. Amol. M., Bhairav, B.A., and Saudager, R.B., 2017, Co-Processed Excipients for Tabletting: Review Artikel, Res J Pharm and Tech., 10(7): 2427-2432
22. Atul, P., Subrata, K., and Ganga, S., 2022, A review on co-processed excipients: a novel approach in formulation development. IJRAPI., 3; 25-41
23. Bansal, AK, and Nachaegari, S, K., 2014, Co processed excipient for solid dosage form. Pharm Technol., 2; 52-64.
24. Bin, L. K., Gaurav, A., and Mandal, UK, 2019, A Review on Co-Processed Excipients: Current and Future Trend of Excipient Technology, Int J Pharm Pharm Sci., 11 (1); 1-9.
25. Bolhuis, G. K., Veen, B., Wu, Y. S., Zuuraman, K., and Frijlink, H. W., 2019, Compaction mechanism and tablet strength of unlubricated and lubricated silicified microcrystalline cellulose. Eur J Pharm Biopharm 59:133–8.
26. Desai, U., Chavan, R., Mhatre, P., and Chinchole, R., 2012, A Review: Coprocessed Excipients, Int J Pharm Sci Rev and Res., 12, (2); 93-105
27. Franc, A., Vetchý, D., Vodáčková, P., Kubaľák, R., Jendryková, L., Goněc, R., 2024, Co-processed excipients for direct compression of tablets, Ces. slov. Farm. 67; 175–181
28. Galbraith, S.C., Cha, B., Huang, Z., ,Park, S., Liu, H., Meyer, R.F., Flamm, M.H., Hurley, S., Zhang-Plasket, F., and Yoon, S., 2019, Integrated modeling of a continuous direct compression tablet manufacturing process: A production scale case study, Powder Technology, 354; 199–210.
29. Gohel, MC, 2022, A review of co-processed directly compressible excipients, J Pharm Pharmaceut Sci., 8 (1); 76-93.
30. Gohel, MC, and Jogani, PD, 2019, A review of co-processed directly compressible excipients. J Pharm Pharm Sci., 8; 76-93.
31. Hauschild, K., and Picker, K. M., 2023, Evaluation of a new co-processed compound based on lactose and maize starch for tablet formulation, AAPS Pharm Sci., 6:1-12.
32. Lan, Y., 2008, A New Excipient for Fast Disintegrating Oral Dosage Forms, Pharma Ingredients & Services, BASF
33. Nagendrakumar, D., Raju, S.A., Shirsand, S.B., and Para, M.S., 2019, Design of fast dissolving granisetron HCL tablets using novel coprocessed superdisintegrants, J Biosci Technol., 1; 8-14.
34. Nofrerias, I., Nardi, A., Suñé-Pou, M., Suñé-Negre, JM, García-Montoya, E., Pérez-Lozano, P., Ticó, JR, and Miñarro, M., 2023 , Comparison between Microcrystalline Celluloses of different grades made by four manufacturers using the SeDeM diagram expert system as a pharmaceutical characterization tool, Powder Technology, 342; 780–788
35. Rojas, J., and Kumar, V., 2021, Comparative evaluation of silicified microcrystalline cellulose as a direct compression vehicle, Int J Pharm. 416(1); 120-128
36. Satish, KN, and Arvind, KB, 2023, Coprocessed Excipients for Solid Dosage Forms, Pharmaceutical Technology, Januari, 52-64

37. Saiga, l. N., Baboota, S., Ahuja, A., and Ali, J., 2022., Microcrystalline Cellulose as a Versatile Excipient in Drug Research, J Young Pharm, 1; 6-12
38. Steele, D. F., Tobyn, M., Edge, S., Chen, A., and Staniforth, J. N. 2018., Physicochemical and mechanical evaluation of a novel high density grade of silicified microcrystalline cellulose, Drug Dev. Ind. Pharm., 30; 103–109
39. Thulluru, A., Madhavi, C., Nandini, K., Sirisha, S., and Spandana, D., 2019, Co-Processed Excipients: New Era in Pharmaceuticals, Asian J. Res. Pharm. Sci. 9(1): 01-05.