THE EXCIPIENTS USED IN THE NON-COATED TABLETS - A REVIEW.

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Abstract
In modern drug technology excipients fulfill many important roles: antiadherents, binders, disintegrants, fillers, flavours, lubricants, etc. They can modify many properties of tablets including disintegration time, substance release place (stomach, intestine) and time (fast or slow release, non-modified), improvement of taste and flavor, etc. There are many scientific reports that can help choose suitable excipients to produce tablets that have desired properties. That paper was created to arrange knowledge about them.

Key words: excipients, drug technology, tablets

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Introduction
Tablets preparation without excipients is very difficult, if not impossible. Only symmetric molecules (linear or tetragonal) can be used to produce tablets without excipients (e.g., sodium chloride, hexamine, calcium oxide, magnesium oxide, sodium bromide and sodium iodide). Substances with monoclinic crystal system are tableted in the longitudinal direction, but so produced tablets can disintegrate easily, therefore, a selection of appropriate excipients is required [1].

Pifferi et al. [2] believe that the traditional concept of the excipients used in solid dosage forms, acts as antiadherents, binders, disintegrants, fillers, flavours, lubricants, etc. However, their qualification to one of the above groups is often impossible, because most of them fulfill more than one function [4].

Importance of excipients can cause more drug side effects. Ursino et al. [3] gave as an example of the soybean oil use in some generic drugs containing omeprazole. There were two cases of anaphylaxis a few minutes after taking the capsules. The authors pointed the marginalization of excipient’s side effects caused in combination with specific medicinal substances, lack in description of possible interactions in leaflets and drug’s package. Excipients added to the solid dosage forms, acts as antiadherents, binders, disintegrants, fillers, flavours, lubricants, etc. However, their qualification to one of the above groups is often impossible, because most of them fulfill more than one function [4].

Formulation of proper dosage form have specified requirements of excipients used, especially for a modified non-coated tablets. One of them are orally disintegrating tablets (ODT), which are a solid dosage form that disintegrate in mouth upon contact of saliva. Therefore it is friendly to patients and ideal drug form for children and elderly patients. According to Al-khattawi [5] the key excipi-
ents for ODT are: sucrose, mannitol, xylitol, sorbitol, maltodextrin. Commonly are also used: cellulose derivatives, starch derivatives, polyvinylpyrrolidone, croscarmellose, sodium starch glycolate. Second special group of non-coated tablets are vaginal tablets. Genc et al. [6] proposed use of methylcellulose, poly(acrylic acid), carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose as an appropriate excipients for vaginal tablets with acyclovir. According to Valenta [7] the best excipients for that dosage forms are: chitosan, cellulose derivatives, hyaluronic acid and derivatives, pectin, tragant, starch, poly(ethylene glycol), sulfated polysaccharides, carrageenan, sodium alginate and gelatine. Whereas in effervescent tablet formulations there are commonly used: citric acid, tartaric acid, fumaric acid, mannitol, sodium citrate, sodium lauryl sulphate and sodium benzoate [8].

Fillers

Fillers are used to produce tablets with desired size and mass. Good fillers should have a suitable flowability, density, poor moisture absorption, chemical indifference and taste accepted by patients. The most common fillers are: lactose, mannitol, glucose, saccharose, sodium chloride, starch, cellulose and starch derivatives [9, 10].

Lactose is a disaccharide composed of D-glucose and D-galactose bond interconnected 1,4-β-glycosidic bond. It exists as two isomers, the alpha form (α) and beta (β). Lactose is easily soluble in water, very slightly soluble in ethanol, and practically not soluble in organic solvents. It is mainly used as a filler in the tablets obtained by direct compression (as in an amount greater than 50%). Often to the tablets with lactose addition of disintegrants is needed, because lactose extends the disintegration time and hardness of tablets [10]. Kuno et al. [11] compared lactose, which has a high melting point and xylitol (sugar with a low melting point) as an excipient for fast release tablets. Tablets containing lactose had improved physical properties, such as hardness and abrasion resistance, but simultaneously their disintegration time is extended. The authors found that tablets with lactose have better storage characteristics and are resistant to heat, while tablets with xylitol disintegrated immediate in mouth.

Mannitol is a sweet taste sugar alcohol derived from manna from Fraxinus ornus, but now is produced synthetically. It is easily soluble in water and glycerol, slightly soluble in ethanol and not soluble in organic solvents. In the drug technology it is often added to sublingual tablets as a filler and binder (5-25%) [12]. It can not be used in patients with anuria and congestive heart failure [13]. Nachajski and Zgoda [14] developed a sublingual tablets containing Echinacea dry extract and different amounts of mannitol and sorbitol. Better physical properties such as hardness, friability and disintegration time had the formulation with: Vivasol (croscarmellose sodium), magnesium stearate, Vivapur 12 (microcrystalline cellulose), mannitol, crospovidone XL 10 (crosپovidone) and citric acid. Worse physical properties had tablets with: Prosolv SMCC 90 (microcrystalline cellulose, colloidal silica, anhydrous silica), Prosolv HD 90 (microcrystalline cellulose, colloidal silica, anhydrous silica), Vivapur 200 (microcrystalline cellulose).
Binders

Binders consist of few groups, such as wetting agents (that can lowered the surface tension of a liquid, e. g. polysorbates, sorbitan esters), dry binders (e. g. pregelatinised starch, cross linked polyvinylpyrrolidone), solution binders (e.g. polyvinylpyrrolidone, cellulose derivatives), soluble in water/ethanol mix agents (e. g. polyvinylpyrrolidone). Binders cause cohesive mixture of powders, which provides them with adequate compressibility and durability. The desired disintegration time can be obtained using a suitable concentration and the type of binder, in the appropriate proportions with the disintegrants. They are used also in order to increase the mechanical strength of the tablet. Such properties usually contain polymers with disordered structure [15]. To the whole binders group can be classified many substances: ethanol, acetone, isopropyl alcohol, gelatin, gum arabic, sucrose, glucose, potato starch, zein or ethylcellulose [16]. In addition, binders have the ability to reduce the distance between the molecules of the substance contained in the tablet masses, so intermolecular bonds become stronger [17].

Polyvinylpyrrolidone (PVP) is a hygroscopic, odorless white powder with broad molecular weight difference (from 2 500 to 1 000 000). It is easily soluble in most polar solvents, both inorganic and organic, however is not soluble in nonpolar solvents [18]. PVP is often used in wet granulation as a binder in the form of aqueous or ethanol solutions (0.5-5%). Tablets containing polyvinylpyrrolidone as a binder have high mechanical strength, are not sensitive to moisture and tend to have a short disintegration time. Additionally, it can be used as a filler, usually in an amount of 10-25% [19]. Garekani et al. [20] studied the effect of different types of PVP (from 2 000 to 50 000) on the properties of paracetamol tablets. Tablets with PVP 10 000 and 50 000 had a very high resistance against crushing, even after application of high pressure compression. The best dispersion of the active substance had tablets containing polyvinylpyrrolidone 10 000. The weakest results were observed in the tablets containing PVP 2000.

Disintegrants

Disintegrants are added to the tablet mass in order to accelerate the disintegration time of the tablets. The disintegration time is one of the most important factors, that determine the availability of a drug from tablet. Disintegrants are added to the solid dosage forms in order to facilitate their disintegration into smaller particles after contact with gastric or intestinal juice. Substances that cause a very rapid disintegration of the tablet, by repeatedly increasing of its mass are called superdisintegrants [21]. They are usually added in an amount of 1-10%, e. g.: croscarmellose, crospovidone and sodium starch glycolate [22]. Depending on the type and amount of disintegrants, the disintegration time of the tablets may change. There was a experience carried out by Preetham et al. [23], who compared the disintegration time of the tablets with acetaminophen containing different disintegrants. The disintegration time of the tablets with croscarmellose sodium was 4.8 min. Tablets containing sodium starch glycolate disintegrated after 4.2 min. After about 3.4 min. disintegrated tablets composed
of polyplasdone XL, only a little later disintegrated tablets with polyplasdone-XL-10 (3.6 min). The study showed that the tablets of polyplasdone XL and polyplasdone XL-10 had a shorter disintegration time than the corresponding tablet with croscarmellose sodium and sodium starch glycolate. Ideal disintegrants should have the following characteristics: poor solubility, good hydration capacity and flow properties, inability to form complexes with drugs [24]. Disintegrants such as starch derivatives, polyvinylpyrrolidone, croscarmellose or sodium starch glycolate are very important part of ODT, which are characterized by rapid disintegration [5].

Starch is found mainly in fruits and roots of plants such as corn, potato, wheat, cassava and rice. Mostly starch is used as a filler, a disintegrant, aqueous solutions (5-20%) are used as binders [25]. Potato starch (Solani Amylum) exhibits the best disintegrants properties (29%), compared to 5-6% of rice or corn starch. The starch may also be used as a glidant, adsorbent or hydrophilizing substance [26]. Many investigations were carried out using different types of starch. Onofre et al. [27] studied the effect of the structure and chemical modification of starch in the sustained-release tablets. More effective were corn and potato starch than Hylon starch. Best release of the tablets showed potato starch, followed by corn starch, while the worst results had kind Hylon. Sikora and Krystyjan [28] studied the effect of polysaccharide hydrocolloids (e.g. guar gum) on different types of starch. Such connections improve the physicochemical properties and are often combined in the food or pharmaceutical industries. They found that products prepared by first dissolving the ingredients and adding them to the liquid powders had worse physical and chemical properties. That was related to the inhibition of swelling and filling of the starch granules.

Microcrystalline cellulose has various particle size which is indicated by the appropriate symbols, such as Avicel PH 101 (particle size of about 50 microns) and Avicel PH 102 (particles of approximately 100 microns) etc. Microcrystalline cellulose is a polysaccharide composed of D-glucose linked together with β-1,4-glycosidic bond. Added to tablets it acts as a filler, binder and disintegrant. Microcrystalline cellulose has good physical and rheological properties, including moisture retention, which is used for preparation of pellets by extrusion and spheronization. Microcrystalline cellulose is often used for the manufacture of pharmaceuticals, because of the low cost and lack of tendency to interact, often used as an excipient in generics [29, 30].

Croscarmellose sodium (Ac-di-sol) is a crosslinked sodium carboxymethylcellulose, obtained by mixing sodium monochloro acetate with alcalicellulose. Croscarmellose sodium is present in varying degrees of polymerization ranging from 200 to 1000. It is insoluble in water, but has swelling properties and can therefore significantly increase its volume in water. It is a stable substance, although it is hygroscopic, so it must be stored in a tightly closed container in a cool, dry place [31]. In the drug technology it is mainly used as an aqueous solutions of 2-6%, as a binders for wet granulation, or as a powder for direct compression. As a disintegrating agent is
usually added in an amount of 2-3% (up to 5%). The addition of larger amounts may cause difficulty in water penetration into the tablet, which may increase their hardness [10, 32]. Vadas et al. [33] showed that the disintegration time of tablets containing croscarmellose sodium as a disintegrant was independent of the pH from dissolution medium used.

Crospovidone is a crosslinked polyvinylpyrrolidone, insoluble in water, acids and alkali, which is often used as a tablet disintegrant. It is chemically inert and forms a reversible complex with many substances [34]. Crospovidone is classified as a superdisintegrant, which is often used in production of tablets, granules and pellets, typically used at a concentration of 1-3%. Added to tablet provides their rapid breakdown, increases the strength of tablets and reduces their fragility [35]. Sallam et al. [36] examined the effect of disintegrants on the disintegration time of tablets containing terfenadine and calcium carbonate. Tablets with crospovidone showed the best properties, a little worse had tablets with Ac-di-sol and Primojel (sodium starch glycolate) and the worst one had tablets with hydroxypropyl derivatives. Perissutti et al. [37] studied the effect of the addition of crospovidone on the disintegration time for tablets containing carbamazepine. Tablets contained also polyethylene glycol PEG 4000 as a binder and lactose as a filler. Tablets met pharmacopoeial standards, the addition of crospovidone assured gradual, but fast disintegration.

Colloidal silicon dioxide is a fluffy white powder, odorless and tasteless. It is obtained by flame hydrolysis of silicon tetrachloride. It is chemically inert, insoluble in water, acids and alkali. Due to the presence of silanol (Si-OH) and siloxane groups (Si-O-Si) it can absorb water up to 40% of its volume. It is often used in tablets coating and capsules [6]. Silicon dioxide is often used in an amount of 0.05-1% in order to improve flowability and 1-2% as a disintegrant, which also increases the hardness of tablets, it is sometimes used as a lubricant [38]. Wan and Prasad [39] produced tablets with the sulfonamide, methylcellulose as a binder and various kinds of disintegrating agents (colloidal silicon dioxide, crospovidone and sodium starch glycolate at different concentrations (1.25-5%). Disintegration time of tablets prepared depended on the nature of disintegrant used. Tablets containing higher concentrations of methyl cellulose and colloidal silica had longer disintegration time than the tablets containing sodium starch glycolate or crospovidone.

Antiadherents
Antiadherents are added to the tablet formulation in order to increase its flowability, reduce friction and improve the properties of powders during the tablets compression. These substances prevent sticking of the tablet to the compression matrix [9]. Most of them is water-repellent, and therefore prevent adhesion of powder particles during tableting, reducing the friction. Antiadherents are mostly used in amount to 1%, as too large amount may modify the disintegration time, solubility, and bioavailability of the tablets [40]. Excessive addition of them causes weakening of intermolecular bonds, which may adversely affect the strength of tablets, it is why they should be added to them in small quantities.
ents includes magnesium stearate, colloidal silica, talc and starch [10, 41].

Magnesium stearate is the most frequently antiadherent used (as well as calcium and aluminum stearate) in tablets. It is insoluble in water, ethanol, but it is easily dissolved in benzene. It is mostly used in an amount of 0.5-1%. However, it may extend the time of tablet’s dissolution and worsen the hardness [42]. Late et al. [43] have tried to determine the best concentration of magnesium stearate in tablets. The tablets contained also leucine, glycerol and stearic acid. The concentration of magnesium stearate was very important for hardness and disintegration time of tablets. Addition of magnesium stearate at a concentration of 1.5% caused the disintegration time of tablets equal to 23.4 sec. and the hardness of 1.42 kg. Magnesium stearate reduces the hardness of the tablet, which is associated with the weakening of intermolecular bonds. As shown in the experiment carried out by Zuurman et al. [44] sorbitol additive does not increase the hardness of tablets containing magnesium stearate. In turn, the tablets containing magnesium stearate at 0.5% concentration, in combination with microcrystalline cellulose showed significant improvement in hardness and other physical properties. Marwah and Rubinstein [45] tried to determine the best ratio of magnesium stearate and magnesium palmitate for use in the form of a powder mixture. Best gliding properties showed a mixture containing 2.5% of magnesium stearate and 7.5% of magnesium palmitate.

Sodium stearyl fumarate is widely used as an antiadherent agent in tablets and capsules at a concentration of 0.5-2%. It is less hydrophobic than magnesium stearate and stearic acid. Formulations containing sodium stearyl fumarate have a faster disintegration time than the corresponding ones with magnesium stearate [46]. Schindler et al. [42] compared the physical properties of tablets containing sodium stearyl fumarate and magnesium stearate. Sodium stearyl proved to be more versatile and does not have the disadvantages associated with magnesium stearate as unequal hardness and disintegration time of the tablets. Compared to tablets containing in its composition as a lubricant, magnesium stearate, sodium stearyl fumarate tablets have better bioavailability of the active substance, a shorter disintegration time and better physical properties of the dosage form [47].

Formulations

There are many examples of tablets containing various excipients formulations in which the physical properties were investigated and the release of their active substances: Sunada et al. [48] received the fast-disintegrating tablets with erythritol, containing as adjuvants croscarmellose sodium (Ac-di-sol), alpha-lactose and microcrystalline cellulose, which were made by direct compression. Asatov et al. [49] investigated the determination of the optimal amount of microcrystalline cellulose in the tablets of papaverine. They studied the nine rules with a different concentration of microcrystalline cellulose, potato starch and magnesium stearate. The best physical properties and release profile had a recipe containing 83% microcrystalline cellulose, 3% potato starch,
1% calcium stearate and 3% aqueous solution of methylcellulose as a binder. Kuno et al. [11] have produced tablets with lactose, crospovidone and xylitol, and with the addition of one of the two antiadherents - magnesium stearate or sodium stearyl fumarate. Rujivipat and Bodmeier [50] prepared tablets containing acetaminophen, carbamazepine, chlorpheniramine and propanol hydrochloride with excipients: HPMC, Eudragit L (methacrylic acid), lactose and magnesium stearate.

**Conclusion**

Saying that excipients in tablets are as important as the drug substance is a highly true opinion. There are few types of non-coated tablets. Excipients used differ a little in each of them. In most popular non-modified tablets almost all can be used. In ODT the disintegrants played a crucial role, while effervescent tablets can not exist without citric acid or a similar excipient. Excipients not only modify many parameters of tablets, but also play roles such as: antiadherents, binders, disintegrants, fillers, flavours, lubricants, etc.

**Resumo**

Helpsustancoj ludas multajn gravajn rolojn en moderna teknologio: kiel kontraudherigantoj, ligiloj, disintegrantoj, plenumigantoj, gustigantoj, lubrikantoj k.t.p. Li povas modifi multajn ecojn de tablojdoj, inkluzive la tempon ĝis disintegrado, la lokon de la substancellaso (stomako, intestino) au ties tempon (rapida au malrapida ellaso, ne modifita), plibonigadon de gusto k.t.p. Ekzistas multaj sciencaj raportoj kiu povas helpi elekti taugajn helpsustancon por produkto tablojdojn kiu havas la dezirataj ecojn. Tiu ĉi publikigado estis prezentita por disvasti la sciojn pri ili.

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