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REVIEW ARTICLE

Alternative extrusion–spheronization aids

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Abstract

Background: Microcrystalline cellulose (MCC) is the most widely used extrusion–spheronization aid but is associated with several limitations such as adsorption of actives, longer dissolution time, and degradation of some sensitive drugs such as ranitidine. *Objective*: This article reviews a number of natural, semisynthetic, and synthetic agents, such as cross-linked polyvinylpyrrolidone, carrageenan, chitosan, pectinic acid, modified starches, coprocessed MCC, glycerides, chitosan, sodium alginate, and β-cyclodextrin (CD) for their potential as alternative extrusion–spheronization aids to MCC. *Method*: Alternative spheronizing aids were characterized and evaluated based on their intrinsic properties such as solubility, water absorption and retention capacity, rheology, surface properties, binding capacity, drug release, and pellets properties such as sphericity, porosity, and friability with respect to MCC. *Conclusion*: Crospovidone, carrageenan, chitosan, pectinic acid, glycerides, β-CD, and cellulose derivatives are effective alternative spheronizing aids and can be used to prepare pellets without any plasticizer or lubricant. But pellets with polyethylene oxide can only be produced with the use of plasticizer and/or lubricant. However, none of them succeeded to provide the same flexibility in formulation and processing during extrusion–spheronization as observed for MCC (e.g., less water-holding capacity, narrow liquid range providing the correct rheology for extrusion–spheronization, addition of binder required to obtain sufficient mechanical strength).

Key words: *Alternative extrusion–spheronization aid; carrageenan; chitosan; crospovidone; microcrystalline cellulose; Polyplasdone® XL-10; pectin*

Introduction

Pellets are spherical multiparticulates of varying diameter. Pellets as a drug delivery system offer not only therapeutic advantages such as less irritation of the gastrointestinal tract, lowered risk of side effects because of dose dumping, and reproducible drug blood levels but also technological advantages such as better flow properties, less-friable dosage form, narrow particle size distribution, ease of coating, and uniform packing. Different methodologies of pellet manufacturing are spraying on nonperil seeds, pellet layering, wax congealing, and extrusion–spheronization[1].

The most popular method of producing pellets is by the extrusion–spheronization technique because it offers several advantages: ease of operation, high throughput with low wastage, narrower particle size distribution, production of pellets with low friability, incorporation of higher level of actives without producing an excessively large particle and produces pellets that are suited to film coating. Extrusion–spheronization involves several steps such as mixing (uniform mixing of drug and excipients), wet massing (wetting the solid mix by addition of liquid/liquid binder solution), extrusion (forcing the material through an extrusion screen), spheronization (breaking and rounding off the extrudates into spheroids), and finally drying[1,2]. This is a very special process in which the material's property to remain uniformly wet throughout the process is important. The material should be wet enough to be extruded easily but not to that extent that it forms a lump during spheronization. The material should be dry such that it generates fines during extrusion and spheronization. Hence, materials with special physicochemical properties are required for this process.

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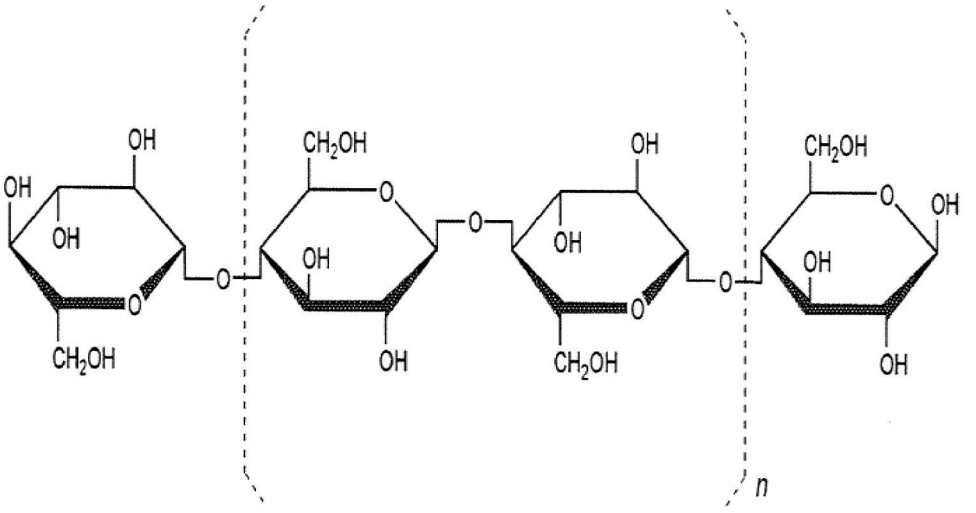

Figure 1. Microcrystalline cellulose.

Microcrystalline cellulose (MCC) (Figure 1) has been considered as an indispensable extrusion–spheronization aid, particularly the commercial grade Avicel® PH-101. This material when dry mixed in adequate concentration with a drug acts as a molecular sponge for the added water, usually forming a plastic mass, which may extrude well before forming well-rounded pellets in a spheronizer[3].

However, MCC formulations show some disadvantages such as the nondisintegration of the pellets, which will result in prolonged, matrix-type dissolution[4]. This undesired property could be overcome by the addition of large quantities of disintegrating aids[5]. Thus, the production of orally fast-disintegrating pellets by extrusion–spheronization using MCC is difficult. In addition some drugs may adsorb to MCC, which will also alter their dissolution time[6]. Some drugs such as ranitidine decompose in the presence of MCC[7]. Therefore, there is an urge for an alternative extrusion–spheronization aid, which can overcome the limitations of MCC.

Ideal properties required in the extrusion–spheronization aids[1,8]

- water insolubility;
- larger water absorption and retention capacity, analogous to a reservoir to achieve optimal rheological conditions for lubrication and surface plasticization required during extrusion and spheronization, respectively;
- cohesiveness;
- sufficiently large surface area for interaction with water and the components of the formulation;
- ability to enhance the drug release.

Alternative extrusion–spheronization aid

This article reviews several alternative extrusion–spheronization aids such as cross-linked polyvinylpyrrolidone, carrageenan, pectinic acid, cellulose derivatives, modified starches, coprocessed MCC, glycerides, chitosan, sodium alginate, and β-cyclodextrin (CD).

Cross-linked polyvinylpyrrolidone

Cross-linked polyvinylpyrrolidone (crospovidone) (Figure 2) is a synthetic, insoluble but rapidly swellable, cross-linked homopolymer of *N*-vinyl-2-pyrrolidone. Unlike other cross-linked polymers, these polymers are synthesized by a unique one-step polymerization process known as 'popcorn' polymerization where the

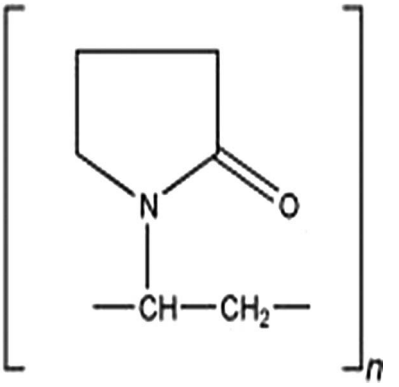

Figure 2. Crospovidone.

cross-linking agent is generated in situ and is thus chemically similar to the bulk of the polymer. This unique manufacturing process results in a densely cross-linked polymer with porous particle morphology. In addition to the referred characteristics these polymers are nonionic and as a result their disintegration performance is not affected by pH changes in the gastrointestinal tract nor form complex with ionic actives. Because they do not form gel, dissolution and disintegration processes are not affected. They are available in several grades differing mainly in the particle size, for example, Polyplasdone® XL is a coarser grade whereas Polyplasdone® XL-10 and Polyplasdone® INF-10 are finer grades[8,9]. Because of rapid disintegration and high compressibility, crospovidone is used as a disintegrating agent in the tablet formulation prepared by wet granulation or direct compression[10–12]. As a disintegrant it is well suited in fast dispersible formulation as it gives a smooth mouth feel and is a harder tablet[13].

Crospovidone possesses an internal reservoir of water that could be mobilized under appropriate pressure ranges. The water holding and controlling capability of crospovidone is possibly related to its cross-linked arrangement, which forms a mesh-like structure around the internal water reservoir. This mesh-like structure possesses both rigidity and flexibility to allow the absorption–release–reabsorption of water during wet massing (moistening), extrusion (lubrication and moistening), and spheronization (surface plasticity). This phenomenon resembles the sponge model proposed for MCC[14].

Appreciable binding with crospovidone occurs at higher water content than that required for MCC, as crospovidone possesses less cohesive properties. Under scanning electron microscopy (SEM) crospovidone appeared to be granular with rough surfaces. On the other hand, MCC particles were elongated, needle shaped, and fractured confirming extra binding strength through mechanical interlocking, which was not pronounced in the case of crospovidone; hence spheronization was carried out at a relatively lower speed to the MCC pellets. Liew et al.[8] compared three different grades, namely, Polyplasdone® XL, Polyplasdone® XL-10, and Polyplasdone® INF-10 as alternative extrusion–spheronization aids and reported that spheronization could be easily accomplished with Polyplasdone® XL-10 and Polyplasdone® INF-10 grades.

The probable reason could be the larger particle size of Polyplasdone® XL, which reduces the overall surface area available for the interaction with water. Crospovidone pellets simulate very favorably compared with microcrystalline pellets. Pellets produced with crospovidone were larger in size with narrow particle size distribution and their disintegration was also faster compared with the MCC pellets.

Carrageenan

Carrageenan (Figure 3) is a hydrocolloid obtained by extraction with water or aqueous alkali from certain species of red seaweed, class *Rhodophyceae*, in particular from *Chondrous crispus*, *Euchema*, *Gigartina stellata*, and *Iridaea*.

The name Carrageenan seems to be derived from the inhabitants of the country of Carraghen, on the south Irish coast, where extracts from red algae for food and medicines were already used since 600 years ago[15]. It consists chiefly of potassium, sodium, calcium, magnesium, and ammonium sulfate esters of galactose and 3,6-anhydrogalactose copolymers. These hexoses are alternatively linked at α-1,3 and β-1,4 in the polymer[16]. The commonly used types are ι- (monosulfate), κ- (disulfate), and λ- (trisulfate) carrageenan, which differ in their degree of sulfation between 15% and 40% and in the position of the sulfate ester group in the repeating galactose units[17]. Furthermore, the inclusion of calcium or potassium salts into the tablet creates a microenvironment for gelation to occur, which further controls drug release[18–20].

The three commercial types of carrageenans are ι, κ-, and λ-carrageenan. They differ in their solubility and swellability in cold water and thus differ in extrusion–spheronization properties. All grades of carrageenans give coherent extrudate. κ-Carrageenan, insoluble in cold water, gives suitable plastic and brittle properties for the spheronization process. In contrast, the soluble ι- and λ-carrageenan resulted in extrudates, which could not be spheronized. Depending on the water content, these extrudates were either too brittle or too elastic to achieve round pellets in the spheronization process; also the addition of calcium, potassium, and sodium ions to the granulation liquid reduced the solubility of the ι- and λ-carrageenan and, consequently, allowed successful spheronization process. By

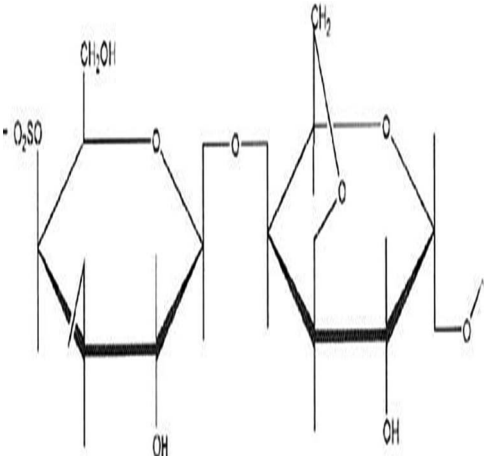

Figure 3. Carrageenan.

the virtue of these findings, insoluble κ-carrageenan seems to be the most suitable type for extrusion–spheronization. Gelcarin® GP-812 NF and Gelcarin® GP-911 NF are two commercial kinds of insoluble and swellable κ-carrageenans. Pellets with 5–98% of Gelcarin® GP-911 NF in powder mixture can be produced. It was possible to produce round pellets in the whole ratio range of κ-carrageenan but 10% was found to be the most adequate. The range of optimal water content was from 46% to 61% for carrageenan whereas only from 32% to 36% for MCC. Carrageenan pellets were similar in size to that of the MCC pellets. A residence time of 5 minutes was found to be robust with regard to the aspect ratio of the pellets in the spheronizer [21,22]. Kleinebudde et al.[23,24] have reported faster release of drug from the κ-carrageenan pellets compared with that from the MCC pellets; this performance was independent of the drug solubility. Also excipients such as maize starch, lactose, dicalcium phosphate dihydrate, mannitol, and various drugs such as acetaminophen, theophylline, mesalamine, and hydrochlorothiazide had minimal effect on the quality of κ-carrageenan pellets (20%, w/w). Thommes and Kleinebudde[24] have studied the effect of four process parameters—screw speed, number of die holes, friction plate speed, and spheronizer temperature—and effect of four drugs—phenacetin, chloramphenicol, dimenhydrinate, and lidocaine hydrochloride—on pellet properties such as shape, size, size distribution, tensile strength, and drug release. The most spherical pellets were achieved in a high yield by using a large number of die holes and a high spheronizer speed. There was no relevant influence of the investigated process parameters on the size distribution, mechanical stability, and drug release. The poorly soluble drugs, phenacetin and chloramphenicol, resulted in pellets with adequate shape, size, and tensile strength and a fast drug release. The salts of dimenhydrinate and lidocaine affected pellet shape, mechanical stability, and drug release properties using an aqueous solution of pH 3 as a granulation liquid. In the case of dimenhydrinate, this was attributed to the ionic interactions with κ-carrageenan, resulting in a stable matrix without disintegration, during dissolution.

The effect of lidocaine is comparable to the effect of sodium ions, which suppress the gelling of carrageenan, resulting in pellets with fast disintegration and drug release characteristics. Thommes and Kleinebudde[24] have compared different types of carrageenans from different suppliers: one ι-, five κ-, and one λ-carrageenan. Four of the five tested κ-carrageenans resulted in pellets with acceptable shapes, sizes, and size distributions using a high drug load of 80% hydrochlorothiazide. These pellets have similar properties over a wide range of water contents ranging from 90% to 105%.

κ-Carrageenan can be a good alternative to MCC because it helps in mitigating few drawbacks associated with MCC such as lack of pellet disintegration and drug absorption. The major disadvantage of pellets formulated with κ-carrageenan is their low mechanical strength and the possibility of ionic interaction.

Pectinic acid

USP 29 describes pectin (Figure 4) as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids[25]. Pectins are a family of polysaccharides in which the polymer backbone mainly comprises α-(1→4)-D-galactouronic acid residues. Pectin has been used in sustained release formulations[26–28], coated pellets[29], and polymeric microspheres[30]. Pectin was earlier explored by scientists for the preparation of beads using ionotropic gelation method (dropping solution of drug and pectin in calcium chloride solution). The drug loading obtained was only 50–60%[31,32]. Pectinic acid with a degree of methoxylation of 4% is almost insoluble in water. The potential of pectinic acid as an extrusion–spheronization aid is elucidated from the fact that formulations containing 20% pectinic acid resulted in spherical pellets. Formulations containing high amounts of pectin need a higher water level to produce pellets. During drying, possible shrinking is therefore more pronounced, leading to smaller pellets[33]. Spherical fast-disintegrating pellets were also obtained for formulations containing up to approximately 80% (w/w) paracetamol and 20% pectinic acid. The aspect ratio of

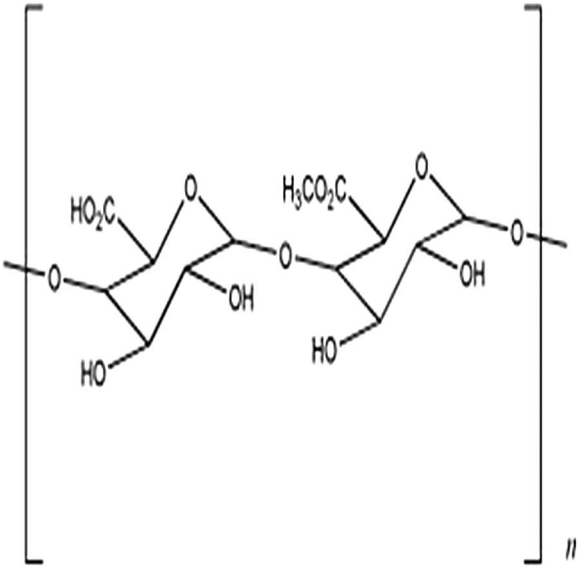

Figure 4. Pectinic acid.

the pellets was below 1.1. The formulation prepared with pectinic acid released around 100% of the drug in 3 hours whereas MCC pellets released only 20% of the drug. The sphericity of the pellets with pectinic acid was more sensitive to the required amount of granulating liquid and to the type and amount of drug than conventional MCC pellets[34]. Pectin molecules with a high degree of free carboxylic acid groups seem to be more sensitive to changes in the granulation liquid. The chemical properties of the pectin—in other words, the degree of methoxylation and amidation—are important for the processability of the formulation. A high degree of methoxylation is not favorable for product formation, but amidation of the low methoxylated pectin seems to have a positive impact on production of short pellets. Amidated pectin extruded with ethanol-containing granulation liquid is well suited for the production of short, nearly spherical pellets. These products were, however, found to be less mechanically stable and more likely to disintegrate. The dissolution rate was relatively high both in 0.1 M HCl and in phosphate buffer saline solution (pH 6.8) for all pectin types[35].

Pectinic acid had a high drug-loading capacity and produced disintegrating pellets that are well suited for fast delivery of low-soluble drug. However, pectinic acid is more sensitive to the type and amount of drug and is, consequently, not as universally applicable as the conventionally used MCC.

Cellulose derivatives

Two cellulose derivatives, hydroxypropylmethylcellulose (HPMC) (Figure 5) and hydroxyethyl cellulose (HEC) (Figure 6), were explored for their feasibility as alternative extrusion–spheronization aids. HPMC is a partly O-methylated and *O*-(2-hydroxypropylated) cellulose[36]. It is available in several grades that vary in viscosity and extent of substitution. HPMC has been widely used in sustained release matrix tablets[37–41]. HEC is a partially substituted poly(hydroxyethyl) ether of cellulose. It is available in several grades that vary in viscosity and degree of substitution[42] and has been used as a film-coating material for tablets[43].

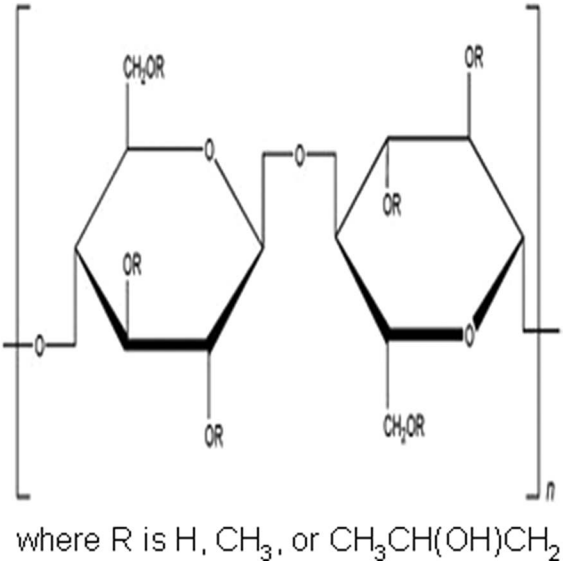

Figure 5. Hydroxypropylmethylcellulose.

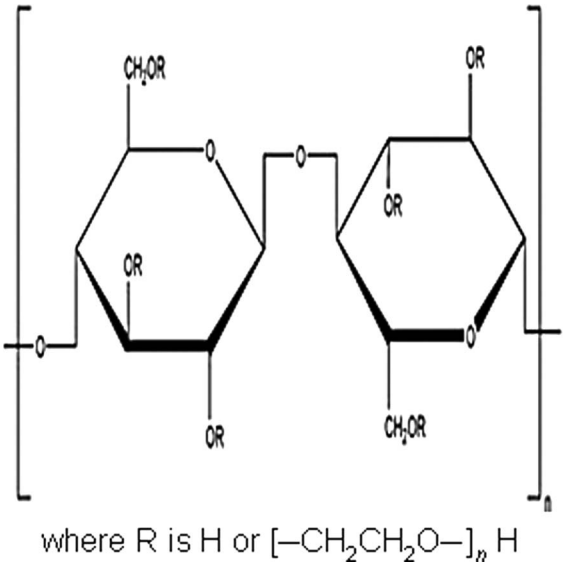

Figure 6. Hydroxyethylcellulose.

Both the cellulose derivatives are water soluble, but insoluble in isopropyl alcohol (IPA) and turn into a tacky mass, owing to their solubility in water. To avoid tackiness, water was substituted using IPA as a granulating liquid. When binding was done with IPA the pellets crumbled after drying, because dissolved hydroxypropyl cellulose was used as binder. Pellets were also prepared using binary liquid (mixture of ethanol and water), and their hardness was higher when the water content increased. After a particular concentration of water in the binary liquid the material starts becoming sticky and sphericity is also reduced. The critical liquid requirement for MCC was much smaller compared with HPMC and HEC. The critical liquid requirement of the three cellulosic materials cannot be correlated with such physical properties as particle size and surface area. The observed difference in the wet massing liquid requirement of the three cellulosic materials may, in part, be due to the difference in their surface properties, such as energetic surface[44].

During dissolution, the HPMC and HEC pellets absorbed water producing a viscous gel matrix and dissolved or eroded, unlike MCC pellets that stayed

intact in the dissolution medium. This behavior may be useful in some specialized applications where complete water solubility of all the formulation excipients is desired. Because the cellulose ethers are available in a wide range of viscosity grades and hydration rates, another possible application of the water-soluble polymers will be in controlled-release dosage form development, where the drug release can be modified from pellets without the application of any rate-controlling membrane coating by appropriate selection of the pellet formulation components.

Polyethylene oxide

The USP 29 describes polyethylene oxide (PEO) as a nonionic homopolymer of ethylene oxide, represented by the formula $(CH_2CH_2O)_n$, in which n represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide[45]. It is highly water soluble with known binding properties that is generally regarded as safe (GRAS status) for use in solid oral human dosage forms[46]. PEO has been used in the preparation of buccal tablets[47] in combination with Carbopol® for the preparation of sustained release tablets[48], for the production of nanoparticles[49], and for the development of pulsatile delivery systems[50].

PEO exhibits binding properties in both the wetted mass and the extrudates, but after spheronization the product was between true spheres and small extrudates, hence it could be considered as a good extrusion aid but not a spheronization aid. These properties led to the use of plasticizers so as to improve the sphericity of the product. Chien and Nuessle[51] suggested the use of polyethylene glycol as a plasticizer for the preparation of pellets. PEG400 was selected because of its structural similarity to PEO. It was hoped that this structural similarity would allow PEG400 in the wetted mass to also act as a plasticizer during the extrusion and spheronization steps. Conceptually, with the applied forces of extrusion, PEG400 would be capable of moving between the strands of PEO to be expressed to the surface. Then, at the surface, the waxy texture of PEG400 would act as an adjunct lubricant to water to reduce surface extrudate damage and dehydration. Methoxypolyethylene glycol was identified as a potential plasticizer similar in chemical structure to PEG400 but less chemically reactive because of the methoxy end group.

Successful production of spherical beads by extrusion–spheronization is dependent upon the production of a wet mass that is cohesive, plastic, and self-lubricating. Because of its chemical nature PEO forms a strong hydrogel in the presence of water, and when this PEO hydrogel is subjected to the shear forces of extrusion, the water is not readily released, thus the mass is called nonself-lubricating. Methoxypolyethylene glycol 550 acts as the best lubricant with PEO and gives quality pellets. Such a combination can be effectively used for the preparation of high drug-loading products with as high as 80% drug loading. Because of the soluble nature of the polymer used, drug release was immediate. This would be an aid of choice when high drug load is required, and MCC cannot be used because of its chemical incompatibility and release-retarding property[52].

Rama et al.[53] have demonstrated the feasibility of producing high-quality beads with a minimal amount of MCC using ethylcellulose and high molecular weight PEO. High molecular weight PEO was used as an extrusion aid and a binder. Each of the batches in this study produced beads that were highly spherical irrespective of the formulation and process variables, suggesting that coarse ethylcellulose is a good excipient for the production of beads by extrusion–spheronization. These beads exhibit the necessary physical and mechanical characteristics for further pharmaceutical processing such as capsule filling and coating.

Modified starches

Starches (Figure 7) are complex polysaccharides. Junnila et al.[54] have prepared pellets using a combina-

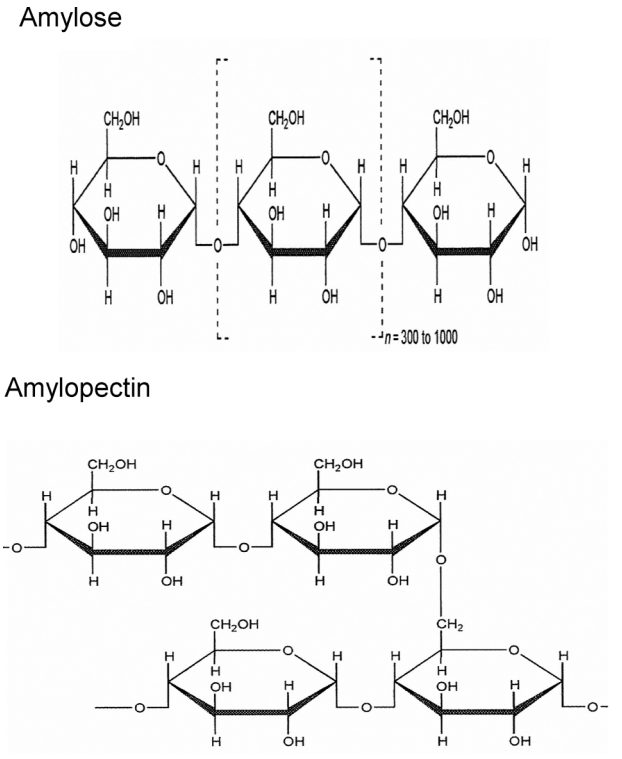

Figure 7. Starch.

tion of MCC and waxy corn starch, but the morphology was not good. Almeida et al.[55] could get spherical pellets using a combination of starch and dextrin. Dukic et al.[56] have used modified starch UNI-PURE®EX[57] as an alternative extrusion–spheronization aid with 25% of drug loading (theophylline). Pellets with good sphericity were obtained only after the addition of binder. The obtained product was with narrow size distribution and high yield. Because this material helps in quick disintegration of the formulation, Dukic et al.[58] have prepared pellets with two poorly soluble drugs hydrochlorothiazide (50%) and piroxicam (2.5%); hydrochlorothiazide (80%) was released in 30 minutes from the starch-based formulation whereas MCC allowed only 40% containing formulation of the drug release in 75 minutes. More than 90% of piroxicam was found to be released in 45 minutes from the starch-based formulation; in the case of MCC the drug release was only 30% in 45 minutes. This significant difference in the release profile was observed because of faster disintegration of starch-based pellets, which ensures faster exposure of poorly soluble drugs to the dissolution medium. Addition of sorbitol as a binder further helped in the release of piroxicam from the formulation (more than 90% in 30 minutes). The sphericity and the friability of the developed pellets were between 1.12 and 1.14 below 0.01%, respectively. Furthermore Dukic et al.[59] have prepared enteric-coated pellets of acceptable sphericity, process yield, and containing modified starch as the main excipient and sorbitol as the binder. However, the extent of drug release during 2 hours in acidic medium ranged from <1% to about 30%, depending on model drug solubility, particle size and concentration, pellet formulation, and drying method as these factors determined the pellet core surface properties. The influence of pellet core surface roughness was reduced by increasing the coating thickness up to 30% of polymer weight gain. Because of pellet disintegration, the drug release in phosphate buffer was immediate for all formulations. Values of $AUC_{0\text{–}72\ hours}$ and C_{max} after the oral administration of piroxicam pellets to dogs were comparable to the values obtained from immediate release capsules.

Despite its similar chemical structure compared with MCC and the promising results for specific starch grades (mechanical strength, sphericity, disintegration, and rapid dissolution of the pellets), starch (derivatives) does not meet all the properties required from the ideal extrusion–spheronization aid as described above: an additional binder had to be incorporated in the formulation to obtain the proper wet mass consistency, and starch-based formulations will be less robust compared with MCC-based formulations because of their narrow range of the optimal water content.

Co-processed microcrystalline cellulose

Levis and Deasy[60,61] have prepared surfactant co-processed size-reduced MCC (Figure 1) using ultrasonic homogenizer. A Suspension of sodium lauryl sulfate and Avicel® PH-101 was passed through the ultrasonic homogenizer multiple times and the product was recovered as dried powder by spray drying. This co-processed material was successfully utilized as extrusion–spheronization aid by those researchers: pellets with 30% of indomethacin with the yield in excess of 80%. Better control of release was observed compared with MCC-containing pellets. The pores in these pellets were in the range 0.1–1.2 μm whereas those in the MCC were in the range 10–20 μm. The higher pore size facilitated the penetration of the dissolution medium, which is the reason for the faster release in the case of the MCC-containing pellets. The drug release retardation was observed only with anionic surfactants whereas other surfactants cause disintegration of the pellets. The amount of surfactant released in the large amount of dissolution medium was well below its critical micelle concentration and thus does not affect the release of the drug.

Podczeck et al.[62] have studied that the addition of sodium carboxymethylcellulose (7LF grade) to the wet cake used to manufacture MCC produces a product that could be of potential benefit in preparing pellets containing high drug loading. Pellets prepared containing 80% of three model drugs with a range of solubility from highly soluble to low solubility were possible for systems to which 6–8% sodium carboxymethylcellulose had been added before spray drying the wet cake used to make Avicel RC 591. They retained the ability of Avicel PH-101 to prepare satisfactory pellets from the two water-soluble model drugs and provided a formulation for the water-insoluble drug for which Avicel PH-101 would not function. The ability of the new types of modified MCC as a formulation aid for the extrusion–spheronization process was found to be related to their ability to hold water when submitted to pressure.

Powered cellulose

USP 29 defines powered cellulose (PC) as purified, mechanically disintegrated cellulose prepared by processing alpha cellulose. It is less crystalline compared with MCC because it is not partially hydrolyzed using mineral acids. Lindner and Kleinebudde[63] have used PC as the alternative extrusion–spheronization aid. Pellets containing 30% of paracetamol were prepared by the authors; the release of the drug from the PC pellets was faster compared with that from the MCC pellets, but the acceptable pellets could be prepared with the aid of a binder-like sodium carboxymethylcellulose. Alvarez et al.[64] have used powdered cellulose for the

preparation of pellets of hydrophobic drug furosemide with 25% and 50% drug loading. The wetting agent required for the PC formulation was much higher than that for the MCC pellets. Similar results were reported by El Saleh et al.[65] Pellets produced with PC showed smaller mean particle size, broader size distribution, and much higher roughness than those produced with MCC. MCC pellets showed clearly better flow properties, attributable to their larger particle size, lower micropore volume, and lower surface roughness. The pellets prepared using PC were more friable, and their drug release was much faster compared with the MCC pellets because of the high micropore volume of the PC pellets. Fechner et al.[66] have studied how molecular and morphological properties of PC and MCC are influenced by extrusion–spheronization process using Fourier transform Raman spectroscopy and environmental SEM. From this study PC was found to be unsuitable as an extrusion–spheronization aid because it requires a lot of binding solution during granulation and it loses the liquid during extrusion and slowly extrusion stops because of the drying of the extrudates. SEM showed that the surface of the PC extrudates were irregular with deep and wide bulges. The MCC extrudates were compact and smooth based on the quantity of the water used for granulation.

Although MCC and PC are similar in their chemical structure they perform very differently as a pelletization aid. Whereas MCC is ideal for the process, PC causes difficulties during extrusion and spheronization. Any model that is intended to explain the role and functionality of MCC as a pelletization aid should be able at the same time to explain the failure of PC despite the chemical similarity of the two excipients.

Glycerides

Glyceryl monostearate (GMS) was used by Basit et al.[7] for the preparation of ranitidine pellets because ranitidine underwent chemical degradation when formulated using MCC. Good spherical pellets with 50% drug, 30% barium sulfate, and 20% GMS with little friability were prepared by the authors. Almost complete drug release was obtained within 15 minutes.

Therefore to explore GMS as an alternative extrusion aid, Newton et al.[67] have prepared pellets with two model drugs: very low-soluble drug,barium sulfate (0.0025 g/L), and low-soluble drug, diclofenac sodium (9 g/mL). In addition, to compare the performance of GMS, the authors have prepared one formulation of each of the model drugs with MCC. It was clearly noticeable that the quantity of water required for being able to prepare the formulations containing MCC was approximately double that required to prepare pellets with GMS. The degree of consolidation, which occurs during the process, is clearly shown by the final porosity of the pellets. The very low levels of porosity obtained with pellets containing high levels of GMS and diclofenac (0.04–0.09) contrast with those that contain high levels of barium sulfate (0.25–0.30). A comparison of the formulations containing GMS and MCC showed that for barium sulfate formulations, the porosity was lower with MCC, whereas it was the reverse for the diclofenac formulations. The aspect ratio of all the formulations was found to be between 1.0 and 1.11. The drug was released (around 40–80%) in an hour, explained by loading and its solubility.

Chatchawalsaisin et al.[68] have prepared pellets by extrusion and spheronization containing MCC and four model drugs with decreasing order of solubility—paracetamol, diclofenac sodium, ibuprofen, and indomethacin—at a 10% level with and without the addition of a range of levels of GMS. It was possible to produce extrudate and pellets with formulations containing the model drugs with 0%, 30%, and 60% of GMS. For the higher GMS content (70%, 80%, and 90%), it was only possible to produce pellets when the drug was sodium diclofenac. The difference in the processing performance of the drugs was not related to the solubility of the drugs in water. The extrudate diameter increased with the level of GMS in the formulation, as well as the median pellet diameter of all the pellet formulations. There was a linear relationship between extrudate diameter and pellet diameter for the formulations containing diclofenac sodium, which did not agglomerate when being spheronized, whereas for the other drugs, this relationship was less clear. Nevertheless, this indicates that the presence of GMS does not change the basic mechanism of the process; the extrudates and the pellets had low levels of surface roughness. The drug release from the pellets was controlled by the solubility of the drug and not by the presence of GMS, which did not retard drug release even when the drugs were dispersed in molten GMS before processing.

Gelucires are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of polyethylene glycol. The first number in the designation of a gelucire product refers to its melting point and the second number refers to its hydrophilic–lipophilic balance on a scale ranging from 1 to 14. Montousse et al.[69] have used Gelucire® 50/02 for the preparation of sustained release pellets of theophylline. When Gelucire®-containing drug was granulated with ethanol, the material could be extruded but not spheronized. The extrusion–spheronization process could be improved with addition of Avicel® (20%) in the formulation. Dupont et al.[70] have prepared spheroids (400 μm) using the extrusion–spheronization process. The extruder used was ram extruder; the materials used for granulation were

Avicel®, Precirol®, Metolose®, and Gelucire®. When the last three excipients were granulated with water, a sticky mass was obtained that could not be extruded; the process was improved by adding MCC. When Gelucire® was granulated with aqueous sodium lauryl sulfate solution, it showed good extrusion–spheronization properties with or without Avicel®. Flament et al.[71] worked on similar lines and studied the incorporation of theophylline (50%) in Gelucire®, which gave good pellets with narrow size distribution without the use of MCC when granulated with aqueous sodium lauryl sulfate solution; Gelucire® did not retard the release of the drug from the formulation (around 90% was released in 1 hour).

Chitosan

Chitosan (Figure 8), a polysaccharide comprising copolymers of glucosamine and *N*-acetylglucosamine, is obtained by partial deacetylation of chitin[72]. Chitosan has been used in direct compression[73] and conventional granulation processes[74]. Chitosan has been used for the preparation of microparticles[75,76] and beads[77]. Chitosan pellets could be prepared by precipitation method using salt solution[78]. Another method applied nonsolvents for the preparation of chitosan pellets[79]. Pellets were prepared by granulating powder mix with the chitosan solution and subsequently the mass was converted into pellets by extrusion–spheronization[80].

Pellets with a maximum content of chitosan (50%) could be produced with demineralized water containing 50% of MCC. Switching from demineralized water to diluted acetic acid as granulation fluid enabled the processability of pure chitosan powder in a twin-screw extruder with no other excipients. With an increasing amount of chitosan in a powder mixture it is necessary to raise the quantity of granulation liquid and the acid concentration to obtain pellets with good sphericity, narrow particle size distribution, low abrasion, and adequate tensile strength. Increasing the acetic acid concentration higher than 0.2 N acetic acid leads to a sticky extrudate or pellets with a rod-like appearance[81]. Pellets can also be prepared using a combination of chitosan and sodium alginate[82]. Chitosan provides pellets of acceptable physical characteristics when 50% (v/v) alcohol/water mixture as binding liquid is employed for the extrusion–spheronization process[83]. Dynamic vapour sorption analysis studies suggest that chitosan can act as a molecular sponge and thus aid in the process of pellet preparation by extrusion–spheronization[84]. Agrawal et al.[85] have prepared pellets without the inclusion of MCC using chitosan as an alternative extrusion–spheronization aid. The pellets were prepared with 15% of chitosan, 10% of HPMC (binder), and caffeine as the model drug. Statistical analysis indicated that formulation variables such as chitosan, HPMC, and water content, and process variables such as spheronizer and extruder speed significantly affected the physical properties of the beads. The bead size decreased with an increase of chitosan content. Beads with high-percentage yield and high sphericity, low friability and porosity, and high density could be obtained at those conditions, which mean high levels of studied formulation variables and low levels of studied process variables. Charoenthai et al.[86] have investigated the influence of the chitosan type on the properties of the pellets. Pellets could be prepared with 60% chitosan, 17.5% MCC, 2.5% sodium alginate, and 20% acetaminophen (model drug). The physical properties and drug release of the obtained pellets depended on the type and amount of chitosan, added sodium alginate, and dissolution media. Moreover, molecular weight of chitosan showed a major effect on the formation and characteristics of the obtained pellets and lower molecular weight chitosan had a better pellet-forming property. Jess and Steckel[87] have studied the effect of the degree of deacetylation of different chitosan grades on process and pellet properties. It was found that the higher the degree of deacetylation (>99%), the more stable is the process, and the properties of resulting pellets such as pellet size, aspect ratio, crushing strength, and friability are better. So, to study the effect of degree of deacetylation on the release, budesonide was used as the model drug by the authors. It was observed that only 53–58% of the drug was released in 9 hours in accordance with the type of chitosan used (degree of deacetylation).

Charoenthai et al.[88] have investigated two types of different molecular weight chitosan as pelletization aid in extrusion–spheronization using water as a granulating liquid. The model drug used was paracetamol. Pellets

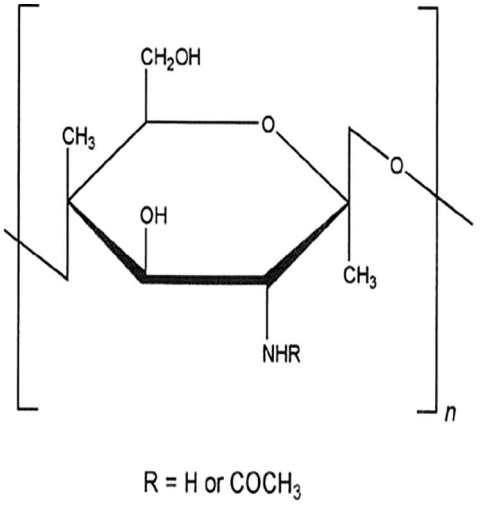

Figure 8. Chitosan.

without MCC could be produced with 60% chitosan, 2.5% sodium alginate, 20% paracetamol, and remainder of lactose anhydrous using water as the granulating liquid. Lower molecular weight chitosan (MW 190 kDa) showed better pellet-forming property. Almost complete drug was released in 20–50 minutes depending on the quantity and type of chitosan used and the type of dissolution medium. The probable reason for successful production of good pellets was the formation of polyelectrolyte complex between chitosan and sodium alginate, which was confirmed using FTIR spectroscopy, DSC, and solid-state ^{13}C CP–MAS NMR spectroscopy.

Sodium alginate

Alginates, a group of anionic polysaccharides, are linear polysaccharides extracted from brown seaweed. They contain varying amounts of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. The residues may vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. The homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks)[89]. The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. One of the most important and useful properties of alginates is the ability to form gels in the presence of some multivalent metal ions such as calcium. The controlled addition of these ions technically leads to insoluble alginate gel formation. The affinity of alginates for calcium ions and their gel-forming properties is mainly related to the overall fraction of G residues, the molecular weight of the polymer, and the calcium ion concentration at the time of gelation. When two G residues are adjacent in the polymer, they form a binding site for calcium. Alginates are of pharmaceutical interest because of their nontoxicity, biodegradability, and biocompatibility[90]. Sriamornsak et al.[91] have prepared pellets containing 30% (w/w) of sodium alginate. The addition of calcium chloride to the granulation liquid reduced swellability of sodium alginate and consequently allowed successful spheronization process.

Sriamornsak et al.[92] have studied the effect of amount and type of calcium salts on the quality of pellets prepared using sodium alginate. Most of the produced pellets were of sufficient quality. Addition of calcium acetate in the formulations slightly enhanced the drug release. A more pronounced effect on increased drug release was seen when the calcium amount was increased. Incorporation of calcium carbonate, however, revealed a lesser pronounced effect.

Sodium alginate does not fulfill all the properties of the ideal extrusion–spheronization aid. The pellets could not be prepared without the aid of MCC. Although the quantity of MCC required for the preparation of pellets was decreased with the aid of calcium salts (calcium salts reduce solubility of sodium alginate by ionic interaction), MCC could be completely removed from the formulation.

β-*Cyclodextrin*

CD, with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complex. Chemically they are cyclic oligosaccharides and available as α-, β-, and γ-CD[93]. The cavity size of α-CD is insufficient for many drugs and γ-CD is expensive. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. But the low aqueous solubility and nephrotoxicity limited the use of β-CD especially in parenteral drug delivery[94].

Villar-López et al.[95] have demonstrated the preparation of pellets with 95% β-CD and 5% triamcinolone acetonide. The pellets had sizes and circularity similar to those formulated with MCC. The pellets showed very fast disintegration. Further coating over the pellets could be accomplished easily by the scientists. Gainotti et al. [96] have explored β-CD as an extrusion–spheronization aid for the preparation of pellets with 90% β-CD. This would be useful for the preparation of pellets of poorly soluble drugs where high amount of β-CD is required.

Conclusion

Extrusion–spheronization is a very effective and the most popular technique for the preparation of pellets. The listed alternative extrusion–spheronization aid could be very useful to overcome some of the problems associated with MCC. The pellets could be easily prepared with crospovidone, carrageenan, chitosan, pectinic acid, glycerides, β-CD, and cellulose derivatives without the need of any plasticizer or lubricant. But pellets with PEO were produced with the use of plasticizer and/or lubricant only. However, none of them succeeded to provide the same flexibility in formulation and processing during extrusion–spheronization as observed for MCC (e.g., less water-holding capacity, narrow liquid range providing the correct rheology for extrusion–spheronization, addition of binder required to obtain sufficient mechanical strength). In addition, the true potential of some of the materials evaluated as extrusion–spheronization aids is difficult to assess based on the available information, because data on essential characteristics are missing (e.g., no dissolution profiles

available as no drug was incorporated in the formulations, maximal drug load not determined). Based on these observations, the authors of this review affirm that each potential extrusion–spheronization aid should be evaluated in relation to all of the properties required for an ideal extrusion–spheronization aid as listed in this article. The conclusion is that MCC is the best extrusion–spheronization aid because of its versatility.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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