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Review article

Production of pellets via extrusion–spheronisation without the incorporation of microcrystalline cellulose: A critical review

A. Dukić-Ott [a], M. Thommes [b], J.P. Remon [a], P. Kleinebudde [b], C. Vervaet [a,*]

[a] Laboratory of Pharmaceutical Technology, Ghent University, Gent, Belgium
[b] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany

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ABSTRACT

Microcrystalline cellulose (MCC) is the golden standard to manufacture spherical particles (pellets) via extrusion–spheronisation since wetted microcrystalline cellulose has the proper rheological properties, cohesiveness and plasticity to yield strong and spherical particles. However, microcrystalline cellulose is not universally applicable due to a number of limitations: prolonged drug release of poorly soluble drugs, chemical incompatibility with specific drugs, drug adsorption onto MCC fibers. Hence, several products have been evaluated to explore their application as extrusion–spheronisation aid, aiming to avoid the disadvantages of MCC and to provide a broad application platform for extrusion–spheronisation: powdered cellulose, starch, chitosan, kappa-carrageenan, pectinic acid, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyethylene oxide, cross-linked polyvinylpyrrolidone, glycerol monostearate. To determine the true potential of the proposed alternatives for MCC this review critically discusses the properties of the different materials and the quality of the resulting pellets in relation to the properties required for an ideal extrusion–spheronisation aid.

1. Pellets as solid dosage forms

Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications [1]. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously, since their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single-unit solid dosage forms [2]:

- Particles smaller than 2–3 mm are rapidly emptied from the stomach regardless of the feeding state of the patient and the influence of gastric emptying rate on the upper gastro-intestinal transit time of pellets is minimised [3], thus lowering the intra- and inter-subject variability of drug plasma profiles compared to single-unit formulations [4].
- The uniform dispersion of a drug into small dosage units reduces the risk of high local drug concentration and their potentially irritating effect on gastric mucosa. Furthermore, drug absorption is maximised and peak plasma fluctuations are reduced [1].
- In the case of coated multiparticulates, every pellet acts as a single drug reservoir with its own release mechanism. Any coating imperfection would therefore only affect the release of a small drug portion, in contrast to complete dose dumping from a single-unit drug reservoir [2].
- Pellets offer the possibility of combining several active components, incompatible drugs or drugs with different release profiles in the same dosage unit.
- Dosage forms with different doses can be produced from the same batch by adjusting the fill weight of the pellets [5].
- Owing to their smooth surface morphology, narrow size distribution, spherical shape and low friability pellets can be easily coated.
- Pellets have good flow properties which ensures reproducible die or capsule filling and consequently good content uniformity [6].

2. Extrusion–spheronisation

Several methods are used for pellet preparation, the most popular being solution/suspension layering, powder layering, direct pelletisation using high shear mixers and conventional or rotary fluid-bed granulators, and extrusion–spheronisation. These pelletisation techniques have been reviewed in detail in a number of papers [5,7,8].

As this review focuses on the extrusion–spheronisation process, this multi-step technique is briefly outlined below. Furthermore,

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, B-9000 Gent, Belgium. Tel.: +32 9 264 80 69; fax: +32 9 222 82 36.
E-mail address: chris.vervaet@ugent.be (C. Vervaet).

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extrusion only refers to wet extrusion; melt extrusion and solid lipid extrusion are not considered. It involves several distinct preparation phases: a uniform powder mixture of drug and excipient(s) is wet massed by the addition of a liquid binder, followed by pressing of the moistened mass through an extrusion screen (extrusion) to form cylindrical extrudates, which are subsequently broken into smaller cylindrical rods and rounded into spherical granules by means of a fast-rotating friction plate (spheronisation) and finally dried. This process is an efficient technique to manufacture pellets (even for formulations with a high drug load), and allows a high throughput based on the continuous nature of the extrusion process when combined with multiple spheronisers operating in parallel or in series. For a comprehensive review of this technique one is referred to [8], detailing the different steps of the process and the influence of the different process parameters at each stage of the extrusion–spheronisation process on pellet quality.

Due to the specific nature of this process not every moistened powder mixture can be successfully extruded and spheronised, and Newton [9] defined the specific requirements for a wetted mass suitable for extrusion and spheronisation based on the pioneering papers from Reynolds [10] and Conine and Hadley [11]. To allow extrusion, a cohesive plastic mass must be formulated that remains homogeneous during extrusion. The mass must possess inherent fluidity, permitting flow during extrusion and self-lubricating properties as it passes through the die. The resultant strands of extrudates must not adhere to each other, and must exhibit plasticity such that the shape imposed by the die is maintained. The requirements for spheronisation of the cylindrical extrudate are as follows: (a) the extrudate must possess sufficient mechanical strength when wet, yet it must be brittle enough to be broken down to short lengths in the spheroniser, but not so fragile that it disintegrates completely, (b) the extrudate must be sufficiently plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate in the spheroniser, (c) the strands of the extrudates must not adhere to each other in order that particles do not aggregate during spheronisation [9].

3. Microcrystalline cellulose as spheronisation aid

In relation to the above-mentioned requirements of the wetted mass, microcrystalline cellulose (MCC) is incorporated in most formulations processed via extrusion–spheronisation, since it provides the proper rheological properties to the wetted mass [9] for successful extrusion and spheronisation [12]. MCC is the golden standard as extrusion–spheronisation aid based on its good binding properties that provide cohesiveness to a wetted mass containing MCC. Furthermore, it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity [13], thus facilitating extrusion, improving wetted mass plasticity and enhancing spheronisation. Moreover, by controlling the movement of water through the plastic mass, it prevents phase separation during extrusion or spheronisation [14]. Due to these properties MCC-based pellets produced via extrusion–spheronisation have a good sphericity, low friability, high density and smooth surface properties. Furthermore, from a processing viewpoint, relatively wide ranges of water content and processing parameters can be employed to provide pellets with acceptable quality, indicating the robustness of the formulations.

Two models have been proposed to explain the behaviour of MCC during extrusion–spheronisation process:

- In the first model, MCC is described as a 'molecular sponge' [15,16]. The MCC particles are able to retain water in a manner similar to a sponge. During extrusion these sponges are compressed, and water that is squeezed from the internal structures acts as a lubricant. After extrusion, the volume of the sponges expands and they appear dry and brittle, which facilitates the breaking of the extrudates during the initial phase of spheronisation. During the spheronisation phase, the sponges are densified due to collisions between particles and the spheronizer plate and wall, and water facilitates spheronisation of pellets.
- According to the 'crystallite-gel model', MCC particles are broken down into smaller units and even partly into single crystals of colloidal size during granulation and extrusion in the presence of water. The resulting crystallites and porous particles form a coherent gel-like network (with a high fraction of an insoluble solid phase) and immobilize the granulation liquid. Over a particular range of water, which relates to an acceptable gel strength, extrusion and spheronisation becomes possible [7,17].

In spite of its excellent characteristics as an extrusion–spheronisation aid, in several cases MCC is not considered as the excipient of choice for the production of pellets via extrusion–spheronisation:

- Drug adsorption onto the surface of MCC fibers has been reported [18–20].
- Several authors reported the chemical incompatibility of MCC with a number of drugs [21–27].
- An effect of MCC powders originating from different suppliers on pellet properties has been reported [28].
- A prolonged drug release was reported when using poorly soluble drugs in a mixture with MCC [29], which was attributed to the lack of disintegration of MCC-based pellets and to drug dissolution and then diffusion through the intact matrix that generates the square root of time release profiles. The drug/MCC ratio in the powder mixture determined the release of poorly water-soluble drugs, being prolonged if the MCC level was higher [29,30].

The lack of disintegration is not an issue when formulating controlled release pellets where drug release is governed via diffusion through a rate-limiting polymer, but in case of enteric-coated pellets or colon-targeted drug delivery pellet disintegration (and a desired fast drug release on reaching the delivery site) it is an important issue. Furthermore, the lack of disintegration is more serious in case of low soluble drugs compared with more soluble drugs.

4. Alternative excipients for microcrystalline cellulose

To obtain pellet disintegration and/or fast drug release from MCC-based pellets, several strategies have been reported (incorpo-

Table 1
Excipients used in combination with microcrystalline cellulose (MCC) to improve pellet disintegration and/or drug release from MCC-based pellets

Excipients	References
Fillers	
Lactose	[31–36]
Dicalcium diphosphate	[35–39]
Mannitol	[39–42]
Starch and derivatives	[32,43,44]
Glucose	[39]
β-Cyclodextrine	[35,45]
Disintegrants	
Croscarmellose sodium, sodium starch glycolate	[46,47]
Surface active agents	
Sodium lauryl sulphate	[48–52]
Polyethylene glycol	[34,53]
Polysorbate 80, glyceryl and sorbitan mono-oleate, sorbitan mono-palmitate	[43,48]
Glycerol monostearate	[34]
Self-emulsifying systems	[54–56]

ration of water-soluble fillers, disintegrants, surface active agents and cosolvents, Table 1). Pellet disintegration of MCC pellets can also be obtained using alcohol/water mixtures as granulation liquid instead of water as this reduced the mechanical strength of the pellets [57,58]. A higher 2-propanol fraction in the granulation liquid improved pellet disintegration and increased drug dissolution due to less bonding between the particles [58]. However, this method also resulted in pellets with reduced mechanical strength.

To overcome the disadvantages of MCC, research in recent years has been directed towards the evaluation of spheronisation aids with the intention to reduce the level of or completely eliminate MCC from the formulation. This manuscript critically reviews the different papers proposing alternatives for MCC during extrusion–spheronisation and evaluates if these polymers are able to overcome the disadvantages of MCC, while providing a broad application platform and allowing the manufacture of pellets with acceptable quality over a broad range of process parameters.

In an attempt to define the properties required for an excipient intended for the production of pellets via extrusion–spheronisation, Liew et al. proposed the following properties as being important [59]:

- water insolubility
- large water absorption and retention capacity
- binding properties
- sufficiently large surface area for interaction with water and other ingredients in the powder mixture
- ability to enhance drug release.

In this paper, the proposed alternatives for MCC are reviewed with respect to the properties required for an ideal pelletisation aid (Table 2). The structures of the proposed pelletisation aids are given in Fig. 1.

4.1. Biopolymers

4.1.1. Powdered cellulose

Powdered cellulose is produced from the same starting material as MCC. In contrast to MCC, the partial hydrolysis by using acids prior to drying is missing. This retains a higher degree of polymerization (DP) and a lower crystallinity index compared to MCC. While MCC is hydrolysed reaching the level-off DP of about 200–350, the chains of powdered cellulose contain different crystalline and amorphous parts. Lindner and Kleinebudde (1994) evaluated the use of powdered cellulose as pelletisation aid [61]. In contrast to MCC formulations, it was necessary to include a binder polymer in the wet massing liquid. Pellets with 30% paracetamol were produced. Pellets prepared with powdered cellulose had a higher porosity, and were less spherical compared to those prepared with MCC. The dissolution from pellets with powdered cellulose was slightly faster, although the pellets did not disintegrate. Powdered cellulose resulted in pellets having a lower quality and without advantage over MCC. It was reported that pellets formulated with powdered cellulose were difficult to prepare since powdered cellulose required more water for extrusion, but its water holding ability was lower. Due to water movement during extrusion the material inside the extruder was compressed, resulting in a dry mass which blocked the extruder [62,63]. This phenomenon is especially important when using high fractions of powdered cellulose. Alvarez et al. compared powdered cellulose with MCC and included 25% and 50% furosemide as a model drug [64]. Compared with MCC the pellets with powdered cellulose showed a higher porosity, surface roughness and friability. The size distribution was broader. The release of furosemide was faster from pellets based on powdered cellulose. Overall, powdered cellulose cannot be considered a suitable alternative for MCC if compared with other suggested pelletisation aids.

Although MCC and powdered cellulose are similar in their chemical structure they perform very differently as pelletisation aid. While MCC is ideal for the process, powdered cellulose causes difficulties during extrusion and spheronisation. Any model, which is intended to explain the role and functionality of MCC as pelletisation aid, should be able at the same time to explain the failure of powdered cellulose in spite of the chemical similarity of the two excipients.

Table 2
Properties required for an ideal pelletisation aid

Properties required for an ideal pelletisation aid
• yielding pellets with spherical shape, narrow particle size distribution, smooth surface, sufficient mechanical strength, low friability and desired release characteristics
• allowing robust processes with high yield
• appropriate for formulations with many (ideally all) drugs
• suitable over a broad drug concentration range, especially at high drug loading of at least 80%
• pure water can be used as wet massing liquid
• no additional excipients are required in the formulation
• wide concentration range of wet massing liquid possible

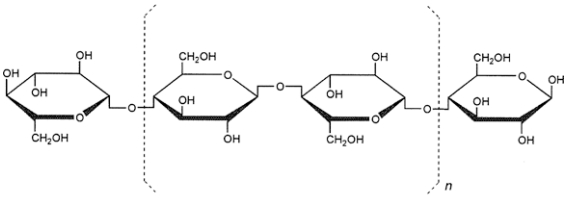
4.1.2. Starch (derivatives)

Already in 1984, O'Connor et al. reported the unsuccessful production of pellets via extrusion–spheronisation using starch (native and pregelatinized) as the main excipient in the formulation [65], and several authors reported on the use of starch as a binder [48,66,67] in formulations with MCC. Otsuka et al. used a mixture of starch (27%, w/w) and lactose (63%, w/w) to produce pellets with 10% (w/w) of theophylline as a model drug. Furthermore [32], Junnila et al. reported on using up to 30% (w/w) native starch, combined with MCC and 2.5% (w/w) of anhydrous theophylline [43]. However, addition of polysorbate 80 as a surface active agent was needed to improve wetting and plasticity. The same authors in another study introduced waxy maize starch as a co-filler in pellets containing MCC and anhydrous theophylline [44]. It was possible to produce pellets containing up to 50% waxy maize starch. However, pellet sphericity expressed by aspect ratio (AR), the ratio of the longest Feret diameter and its perpendicular Feret diameter was at the limit of acceptability. Sphericity was considered acceptable in case of pellets with AR values between 1 (an ideal sphere) and 1.2, as recommended by Kleinebudde [68] and Chopra et al. [69]. In addition, the data on drug release were not provided. Almeida Prieto et al. reported on using native maize and wheat starch to prepare pellets without MCC [70]. It was possible to produce starch-based pellets only after the addition of waxy maize starch, white or yellow dextrin in concentrations up to 20% w/w. However, no model drug was used and pellet sphericity was poor, except for the ones prepared from the mixtures of starch and white dextrin.

Recently, Dukić et al. reported the application of a specific grade of modified starch for extrusion–spheronisation purposes [71]: a crystalline, high-amylose starch formed by gelatinization of amylose-rich starches, followed by enzymatic debranching of amylopectin molecules and retrogradation of linear amylose chains [72]. This starch grade is insoluble in cold water and due to its crystalline nature it does not swell but freely disperses in cold water. Based on these properties and taking into account the large number of hydroxyl groups (responsible for its high water binding capacity) and small particle size (ensuring a large powder surface area), this type of starch is a potential candidate for use in extrusion–spheronisation as some of the preferred properties listed by Liew et al. [59] can be recognized in this material.

Preparation of high-quality pellets was possible using this starch grade [71], but the incorporation of a binder (e.g. low molec-

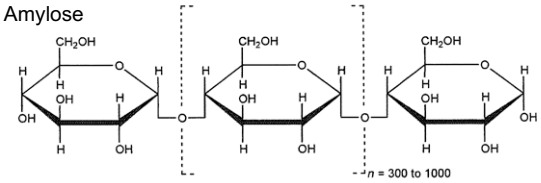
Microcrystalline cellulose and powdered cellulose (polysaccharides)



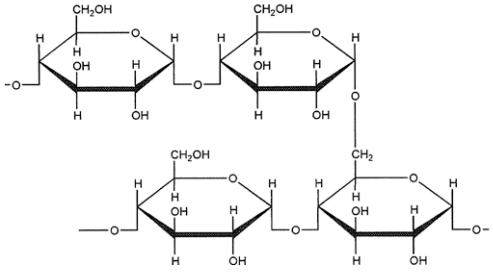
Remark: powdered cellulose has a higher degree of polymerisation (n ~ 500 vs. n ~ 220) and a lower crystallinity compared to MCC.

Starch (polysaccharide)

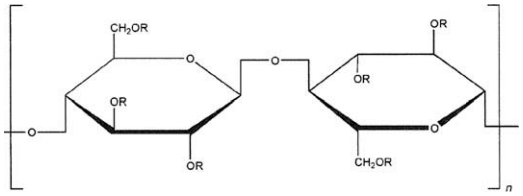
Amylose



Amylopectin



Hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) (semi-synthetic cellulose derivatives)

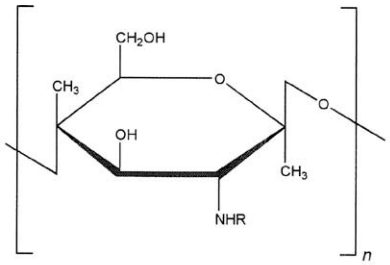


HPMC: R is H, CH_3 or $CH_3CH(OH)CH_2$

HEC: R is H or $(-CH_2CH_2O-)_mH$

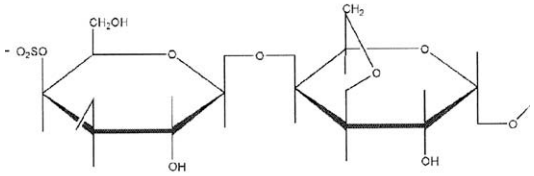
Polyethylene oxide $HO(CH_2CH_2O)_nH$

Chitosan (cationic polysaccharide)

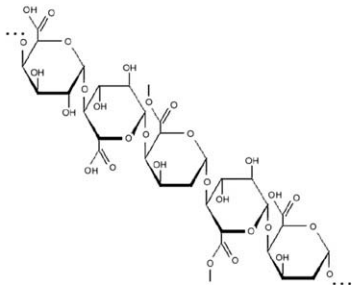


R = H or $COCH_3$

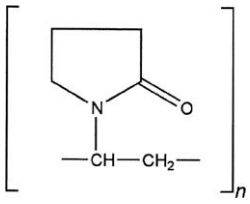
K-carrageenan (anionic polysaccharide)



Pectinic acid (polysaccharide, also in methylated and amidated form)



Crospovidone (the structure of polyvinylpyrrolidone is presented, crospovidone is a cross linked grade of polyvinylpyrrolidone)



Glyceryl monostearate

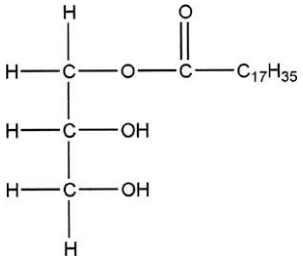


Fig. 1. Structures of the proposed extrusion–spheronisation aids [60].

ular weight HPMC) was required to maintain the integrity of the pellets during spheronisation. Pellets with a high yield (>90% within the 710–1400 μm size fraction), acceptable sphericity (AR < 1.2) and low friability (<0.01%) were produced. Compared to microcrys-

talline cellulose its water holding capacity was approximately two times lower [73], which might explain the narrower concentration range for water that allowed extrusion–spheronisation. The wetted mass consistency of starch-based pellet formulations as determined by mixer torque rheometry was also lower compared to MCC-based formulations, which could explain a narrower optimal spheronisation speed range. Including sorbitol in the pellet formulation increased wetted mass consistency and increased pellet yield. Inclusion of sorbitol as a water-soluble formulation component lowered the optimal water level needed for successful extrusion–spheronisation, allowed the use of a broader water content range for successful spheronisation and improved the surface morphology of dried pellets.

Modified starch was able to significantly increase the drug release by promoting pellet disintegration: Dukić et al. reported the rapid release (100% within less than 20 min) of anhydrous theophylline (25%, w/w) since these starch-based pellets disintegrated within 10 min [71], while in a second study of the same authors [74] immediate release of poorly soluble model drugs (up to 50% hydrochlorothiazide and 2.5% piroxicam) was achieved (more than 80% release after 30 min) due to pellet disintegration within 15 min. Moreover, immediate release of hydrochlorothiazide from starch-based pellets was also observed during an in vivo study performed in dogs, since its pharmacokinetic parameters were not significantly different from a fast-disintegrating immediate release hydrochlorothiazide tablet.

In another study by the same authors the coating properties (using an enteric coating) of starch-based pellets were evaluated [75]. After 2 h dissolution in 0.1 N HCl, the drug release from piroxicam pellets was less than 1% indicating that coating was successfully performed, but the drug release from theophylline pellets depended on the surface morphology of pellet cores. Mercury intrusion porosimetry combined with scanning electron microscopy revealed that surface roughness of the pellet depended on the drying method (oven vs. fluid-bed) and the formulation (incorporation of sorbitol). Hence, enteric coating of theophylline pellets dried in a fluid-bed was only successful (<10% release after 2 h in acid medium) using a higher coating thickness in comparison to pellets dried in an oven (having a smoother surface).

Despite its similar chemical structure compared to MCC and the promising results for specific starch grades (mechanical strength, sphericity, disintegration and rapid dissolution of the pellets), starch (derivatives) do not meet all the properties required from the ideal extrusion–spheronisation aid (Table 2): 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 to MCC-based formulations due to their narrow range of the optimal water content.

4.1.3. Chitosan

The use of chitosan for the production of pellets via extrusion–spheronisation has been reported by several authors in mixtures with MCC [35,76–79] as well as a pure spheronisation aid [80–82]. Chitosan is a polycationic copolymer, consisting of glucosamine and *N*-acetylglucosamine monomers. It is obtained by *N*-deacetylation and limited depolymerisation of chitin, a natural polysaccharide consisting of poly *N*-acetylglucosamine. Due to its cationic character, chitosan has a pH-dependent solubility in water: it is soluble in acidic medium and insoluble in basic medium [78].

In a recent study, Jess and Steckel investigated the influence of the degree of deacetylation of chitosan on the properties of pure chitosan pellets [81]. It was concluded that chitosan with the highest degree of deacetylation (99.9%) and wetted with 0.2 N acetic acid provided the best wetted mass plasticity to obtain pellets with adequate size, sphericity, friability, mechanical strength and surface properties. The drug release of a model drug (0.6% budesonide) was sustained according to a zero-order model. Agrawal et al. (2004) prepared MCC-free pellets using up to 15% (w/w) chitosan and up to 10% (w/w) hydroxypropylmethylcellulose (HPMC) as an additional binder [80]. Pellets disintegrated and the drug (caffeine) release was not sustained. Pellet properties depended on the formulation (chitosan, HPMC and water concentration) and processing variables (extrusion and spheronisation speed). In general, pellets with acceptable yield, size and sphericity, low friability and high density were obtained. In a further study [83], Agrawal et al. (2004) compared MCC and chitosan with respect to their interaction with water. Using differential scanning calorimetry (DSC) and dynamic vapor sorption (DVS) experiments, they concluded that there was no statistical difference between the two polymers to hold and distribute water within the amorphous region of the polymer. It was proposed that chitosan can act as a 'molecular sponge' like MCC. Charoenthai et al. (2007) investigated the influence of formation of polyelectrolyte complex between polycationic chitosan and polyanionic sodium alginate on the quality of MCC-free pellets [82]. Acetaminophen was used as a model drug, while lactose monohydrate was used as a filler. It was possible to produce pellets with fast drug release. As in a previous study by the same authors [79], pellet properties and drug release depended on the molecular weight of chitosan, addition of sodium alginate, filler properties and dissolution medium [82].

With respect to the proposed properties of a spheronisation aid (Table 2), chitosan is not ideal since it requires the addition of either a granulation liquid having a specific pH, a second polymer (e.g. sodium alginate, HPMC) or a binder (HPMC). Furthermore, no data on the maximal drug load were provided and, due to the ionic nature of chitosan, ionic interactions with drugs are possible.

4.1.4. κ-Carrageenan

Garcia and Ghaly developed a method to prepare bio-adhesive pellets by extrusion–spheronisation using carrageenan in 2001 [84]. However, κ-carrageenan was only used as a binding agent as the formulations included a high amount of MCC (>50%) as a pelletisation aid.

In 2005, Bornhöft et al. introduced carrageenan as pelletisation aid for extrusion–spheronisation [85]. The ι-, κ- and λ-carrageenan subtypes were screened for pelletisation behaviour, and κ-carrageenan was found to be a very promising substitute for MCC in pelletisation. A higher requirement of water was observed during extrusion–spheronisation for κ-carrageenan formulations compared to MCC formulations, but κ-carrageenan formulations were more robust with respect to fluctuations in water content. Furthermore, systematic investigations of κ-carrageenan were conducted to examine the effect of other ingredients on the pellet properties. Therefore, four different drugs (acetaminophen, theophylline, mesalamine and hydrochlorothiazide) and four different fillers (lactose, mannitol, maize starch and dicalciumphosphate dihydrate) were varied systematically in 36 formulations [86,87]. All formulations yielded pellets with good shape and size characteristics. Thus, κ-carrageenan was confirmed to be a suitable pelletisation aid. In general, carrageenan pellets had a lower mechanical stability and a faster drug release than pellets made using MCC. The rapid drug release of κ-carrageenan pellets makes wet extrusion–spheronisation applicable to poorly soluble drugs such as hydrochlorothiazide. The slow diffusion-controlled drug release of MCC pellets is highly correlated to the drug solubility, and therefore the time for drug release exceeds the gastro-intestinal passage time for poorly soluble drugs [87]. This effect was overcome by the pellet disintegration using κ-carrageenan as pelletisation aid.

The properties of κ-carrageenan-based pellets were affected by the drying conditions of the pellets as well as by the presence of cations in low concentrations [88]. Thermal decomposition above 70 °C reduced the mechanical strength and increased the dissolution rate

from carrageenan pellets. Calcium ions, however, increased the mechanical strength and reduced the dissolution rate by an ionic interaction with the acid sulfate ester groups of the carrageenan molecule. κ-Carrageenan is a biopolymer extracted from red seaweeds [89], and as such, the commercial κ-carrageenan products may have some variability in the physicochemical behavior. Five different κ-carrageenans from four different suppliers were compared with respect to their pelletisation behavior as well as pellet properties [90], and several differences were observed, e.g. the water binding capacity and the yield point of the carrageenan-gels. However, all κ-carrageenans yielded pellets with suitable size, shape, mechanical strength and drug release characteristics. The effect of the different process variables using κ-carrageenans was recently evaluated [91]. The effect of water content and spheronisation time on pellet properties was comparable to MCC formulations. A larger number of die holes in the extrusion screen and a high spheroniser speed resulted in a more spherical pellet shape. The screw speed and the spheroniser temperature were insignificant under the experimental conditions. Furthermore, an ionic interaction between the alkaline drugs dimenhydrinate and lidocaine-hydrochloride and κ-carrageenans was observed in this study, which might be a limitation of this pelletisation aid.

κ-Carrageenan is an alternative pelletisation aid for MCC, which is applicable in several formulations since the use of κ-carrageenan mitigated several drawbacks of MCC such as lack of pellet disintegration and drug adsorption. The major disadvantage of pellets formulated with κ-carrageenan is their lower mechanical stability and the possibility of ionic interactions. However, κ-carrageenan has a particular position with respect to most MCC substitutes, because there is a dosage form (Clarosip®, Gruenenthal) marketed which uses the advantages of this pelletisation aid.

4.1.5. Pectinic acid

In a series of papers, Tho et al. [92–97] evaluated different kinds of pectins as possible pelletisation aids. Pectin is a partly water-soluble, gel-forming polysaccharide consisting of polygalacturonic acid extracted from apple pomace or citrus peel. Different substitutions at C6 result in the free acid, a methoxylated or amidated product. In addition, the different pectin grades vary in their degree of methoxylation and amidation. Most pectin types are not suitable as pelletisation aid if processed with pure water as wet massing liquid due to the high degree of swelling and the stickiness of the extrudates [92]. However, the addition of additives like ethanol, calcium chloride or citric acid could improve the outcome of the pelletisation process depending on the pectin type [93]. This was attributed to the lower solubility of pectin in the presence of these additives. The influence of the different additives was concentration dependent. It was possible to find quantum chemical descriptors to explain the effect of the additives in the wet massing liquid: the two most important factors being a small molecular size and a strong hydrogen bond forming ability of the additive [95]. The cross-linking of amidated low-methoxylated pectin with calcium ions was analysed further. Due to cross-linking the calcium ions were able to reduce the solubility and swelling of pectin during pelletisation, which resulted in more spherical pellets. Nevertheless, the incorporation of additives itself is a serious drawback of the use of pectins and the pellet properties were not as desired.

The low-methoxylated (4%) pectin derivative is a low soluble pectinic acid. This pectin type was successfully pelletised in combination with lactose and 1% riboflavin as a model drug using water for pelletisation [94]. The resulting pellets were not perfectly round, but the spheronisation step was not optimised. The pellets were mechanically stable and partly disintegrated during dissolution experiments. The release of riboflavin was sufficient. In a further study the drug load was varied from 1% to 80% [96]. Pectinic acid had a high drug loading capacity and produced disintegrating pellets that are well suited for fast delivery of drugs with a low water-solubility. The pellets were also mechanically stable. However, pectinic acid is more sensitive to type and amount of drug and is, consequently, not as universally applicable as the conventionally used MCC.

4.2. (Semi-)synthetic polymers

4.2.1. Hydroxypropyl methylcellulose and hydroxyethyl cellulose

Hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) were evaluated as spheronisation aids by Chatlapalli and Rohera [98]. It was not possible to use water as granulation liquid, since HPMC and HEC are water-soluble polymers and the formation of tacky mass did not allow further processing. However, it was possible to prepare pellets with isopropylalcohol (IPA) as non-dissolving granulation liquid. Due to the low mechanical strength of the dried pellets, it was necessary to include a binder (hydroxypropylcellulose dissolved in IPA) in the formulation. Although rheological characterization of the wetted material using a mixer torque rheometer indicated that the workable liquid range was narrower in case of HEC [99] pellets could be prepared using both polymers, but HPMC-based pellets had a superior quality (friability, surface structure, sphericity). An issue raised by Chatlapalli and Rohera is that the higher lot-to-lot variability in particle size and surface area observed for both cellulose ethers (in comparison to MCC) could compromise the applicability of these polymers for extrusion–spheronisation [100]. Without the availability of materials with tight specifications for these parameters, constant rheological properties of the wetted mass at a constant liquid content cannot be ensured. HPMC and HEC pellets were prepared without model drug by Chatlapalli and Rohera [98], but it is obvious that this approach is not feasible to prepare disintegrating pellets with fast drug release since in contact with water the HPMC pellets absorbed water and turned into a viscous gel-like matrix that slowly dissolved. HEC pellets remained essentially intact in water. Although they swelled significantly, they eroded slowly. This behaviour will most probably result in sustained drug release from HPMC and HEC pellets. Drug release could possibly be modified by using different viscosity grades of these cellulose ethers.

4.2.2. Polyethylene oxide

Polyethylene oxide (PEO) is a high molecular weight polymer of ethylene glycol. Polyethylene oxide has recently been proposed as spheronisation aid in a formulation containing more than 80% pseudoephedrine hydrochloride as water-soluble model drug [101]. Polyethylene oxide, a highly water-soluble polymer, provided sufficient plasticity to the wetted mass. However, low molecular weight methoxypolyethylene glycol (MPEG) acting as plasticizer was needed to improve the self-lubricating properties of the wetted mass. A mass ratio of 2:1:1 for PEO/MPEG/water was used in an experimental design, which studied the influence of drug load (all above 80%) and process variables (feeder, extrusion rate, spheronisation speed and spheronisation time) on pellet yield, sphericity and friability. The processing parameters highly influenced pellet properties: pellet yield ranged from about 56% to 78%, friability from 1.1% to 29.1%, while the roundness score ranged from 1.15 to 1.36 (with 1 representing a perfect sphere). Due to soluble nature of the polymers used, drug release was immediate. Despite their different chemical structures compared to MCC, PEO/MPEG mixtures were assessed as useful for processing via extrusion–spheronisation in case a high drug load is required and the use of MCC is not possible due to incompatibility or incomplete drug release.

4.2.3. Cross-linked polyvinylpyrrolidone

Liew et al. (2005) proposed cross-linked polyvinylpyrrolidone (crospovidone) as pelletisation aid [59]. Crospovidone is a syn-

thetic water-insoluble cross-linked homopolymer of *N*-vinyl-2-pyrrolidone. It is available from different suppliers in different grades concerning the particle size. Crospovidone is mainly used as a disintegrant in tablet formulations. Liew et al. (2005) tested three different grades of crospovidone as pelletisation aids in mixtures with lactose. The binary mixtures included 20% to 30% crospovidone. The coarse grade could not be used as pelletisation aid, but both smaller grades (20 and 32 μm) allowed the production of pellets. Crospovidone was compared to MCC with respect to its ability to control the distribution and release of water during the pelletisation process. Mixer torque rheometry revealed that the consistency of crospividone/lactose mixtures is of lower magnitude compared to MCC/lactose mixtures. Due to their lower cohesiveness the extrudates formulated with crospovidone could not withstand higher shear forces. However, by optimising the water content and the operational variables in a Box-Behnken-Design it was possible to obtain pellets with an aspect ratio of 1.11, and a yield of 74%. The authors attributed a tremendous potential to crospovidone as an alternative to MCC. Unfortunately, information about some essential parameters for a product intended for extrusion–spheronisation (Table 2) are missing: (a) information about the inclusion of drugs is not available since only binary mixtures of crospovidone and lactose were investigated, (b) information about the mechanical properties and disintegration of crospovidone pellets is also not available, (c) it is not clear whether drugs with different properties can be included and to what extent this is possible. Consequently, data about dissolution profiles are missing. These properties are of major importance for the practical application of crospovidone during extrusion–spheronisation. Nevertheless, the missing information does not exclude crospovidone from being possibly an interesting alternative to MCC, but more data are required to assess its true potential.

Recently, Verheyen et al. (2008) have presented results for pellets with crospovidone as pelletisation aid [102]. They confirmed the suitability of the small particle grade of crospovidone as pelletisation aid. Binary mixtures with 10-90% paracetamol or hydrochlorothiazide were extruded and spheronised. It was possible to include up to 70% (w/w) of both drugs into the pellets, while higher drug loads gave no pellets. All pellets had a disintegration time below 40 s with the exception of 70% paracetamol pellets. All pellets showed a fast dissolution: paracetamol was dissolved within 20 min and hydrochlorothiazide within 45 min. The friability was below 1% with the exception of 70% paracetamol (1.4%) and 50% hydrochlorothiazide (1.0%).

4.3. Other materials

4.3.1. Glyceryl monostearate

Initially, glyceryl monostearate (GMS) (in combination with barium sulphate) was introduced as an alternative for MCC for the production of ranitidine pellets via extrusion–spheronisation due to the chemical degradation of ranitidine by means of a complex three-way interaction between drug, MCC and water [21]. It was possible to obtain spherical pellets (containing 50% ranitidine hydrochloride) by completely replacing MCC by a mixture of GMS (20%) and barium sulphate (30%). Drug release from this pellet formulation was rapid (about 80% drug released after 10 min).

Newton et al. further explored the possibilities of GMS (in combination with diclofenac sodium as model drug) to prepare MCC-free pellets [103]. The optimal water content depended on the GMS concentration in diclofenac sodium-containing formulations (more water was required at higher GMS concentration), but compared to MCC-based formulations the optimal water content for GMS formulations was much lower (18.0% and 46.2% for a 10% diclofenac formulation processed with GMS and MCC, respectively). This is a considerable advantage to reduce the drying time after extrusion-spheronisation or when processing water-sensitive drugs. Furthermore, GMS-based pellets were larger compared to MCC pellets and sphericity was acceptable (AR < 1.2). No information about pellet disintegration was provided, but within 1 h about 40 to 80% drug was released from the pellets depending on the drug concentration. Chatchawalsaisin et al. further investigated the potential of GMS as spheronisation aid using several model drugs with varying solubility (drug concentration: 10% w/w) [104]. None of the model drugs (except diclofenac sodium) could be processed without the addition of at least 30% (w/w) MCC, indicating that GMS cannot be used as a broad formulation platform when preparing pellets via extrusion–spheronisation. With increasing GMS content in the formulations, the optimal water level decreased and pellet size increased. Pellet sphericity was acceptable. Drug release depended on drug solubility, being slower if a poor water-soluble drug was used in the formulation.

5. Conclusion

This critical evaluation of the different alternatives proposed for MCC as extrusion–spheronisation aid confirmed that several biopolymers and synthetic polymers are suitable for this application and that their use allows to overcome some of the disadvantages of MCC. However, none of them succeeded to provide the same flexibility in formulation and processing during extrusion–spheronisation as observed for MCC (e.g. less water holding capacity, narrow liquid range providing the correct rheology for extrusion–spheronisation, addition of binder required to obtain sufficient mechanical strength). In addition, the true potential of some of the materials evaluated as extrusion–spheronisation aids is difficult to assess based on the available information, since 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 stress that each potential extrusion–spheronisation aid should be evaluated in relation to all of the properties required for an ideal extrusion–spheronisation aid as listed in this paper.

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