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Non Mcc Polymer as a Pelletisation Aid: A Review

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Abstract

Extrusion spheronization is the widely used method by which the pellets are formulated. Pellets have certain advantages in the development of modified release dosage forms, Because of their regular shape and size they are suitable for coating and encapsulation processes, In addition, pellets may sometimes improve the bioavailability, reduce the risk of dose dumping and decrease local irritations in the gastrointestinal tract. Ideal pelletizing aid for this process is MCC as it possesses suitable rheological properties, cohesiveness and plasticity to yield strong and spherical particles. On the other hand MCC have reported some limitation like, drug adsorption on MCC fiber, prolonged drug release of poorly soluble drug and chemical incompatibility with specific drugs. This review focuses on materials that can totally or partially replace MCC in order to optimize the properties and the quality of pellets produced by the extrusion-spheronization that includes carrageenan, chitosan, pectinic acid, modified starches, sodium alginate, and β-cyclodextrin (CD) for their potential as alternative extrusion–spheronization aids to MCC. 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: None of the polymer studied, proven that much of robustness in formulation of pellets identical to MCC. Some of the polymer discussed forms pellets in combination with MCC or require some plasticizer/lubricant/binder to form good quality of the pellets.

Keywords: Extrusion spheronization, Non MCC, chitosan, carrageenan, modified starches, sodium alginate.

Introduction

Pellets are spherical, free flowing granules with a narrow size distribution between 500 and 1500 μm for pharmaceutical applications [1]. As pellets are multiparticulate drug delivery system it possess following advantages.

➢ Particles smaller than 2–3 mm are rapidly emptied from the stomach irrespective of the feeding state of the patient and the impact of gastric emptying rate on the upper gastro-intestinal transit time of pellets is diminished [2], hence lowering the intra and inter-subject variability of drug plasma profiles compared to single-unit formulations [3].

➢ The uniform dispersion of a drug into stomach reduces the risk of high local drug concentration and their possibly irritating effect on gastric mucosa. Additionally, drug absorption is increased and peak plasma fluctuations are reduced [1].

➢ In the case of coated multiple unit particles, every particle acts as a single unit drug reservoir with its own release mechanism. Only coating imperfection would therefore affect the release of a small drug portion, hence only dose dumping may from single particle not from complete dosage form [4].

➢ Pellets offer the opportunity of combining several active components, incompatible drugs or drugs with different release profile 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 ensure reproducible die or capsule filling and consequently good content uniformity [6].

2. Extrusion-Spheronization

It is a process for preparing pellets with uniform size from wet extrudates. The method involves the following key steps: the dry mixing of the ingredients, in order to achieve

homogenous powder dispersions; wet massing, in which the powders are wet mixed to form a sufficiently plastic mass. an extrusion stage, in which the wet mass is shaped into cylindrical segments with a uniform diameter; the spheronization stage, in which the small cylinders are rolled into solid spheres (spheroids); the drying of the spheroids, in order to achieve the desired final moisture content; screening, to achieve the desired narrow size distribution.

2.1 Extrusion
Extrusion consists in applying pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of the extruder and further shaped into small extrudate segments.
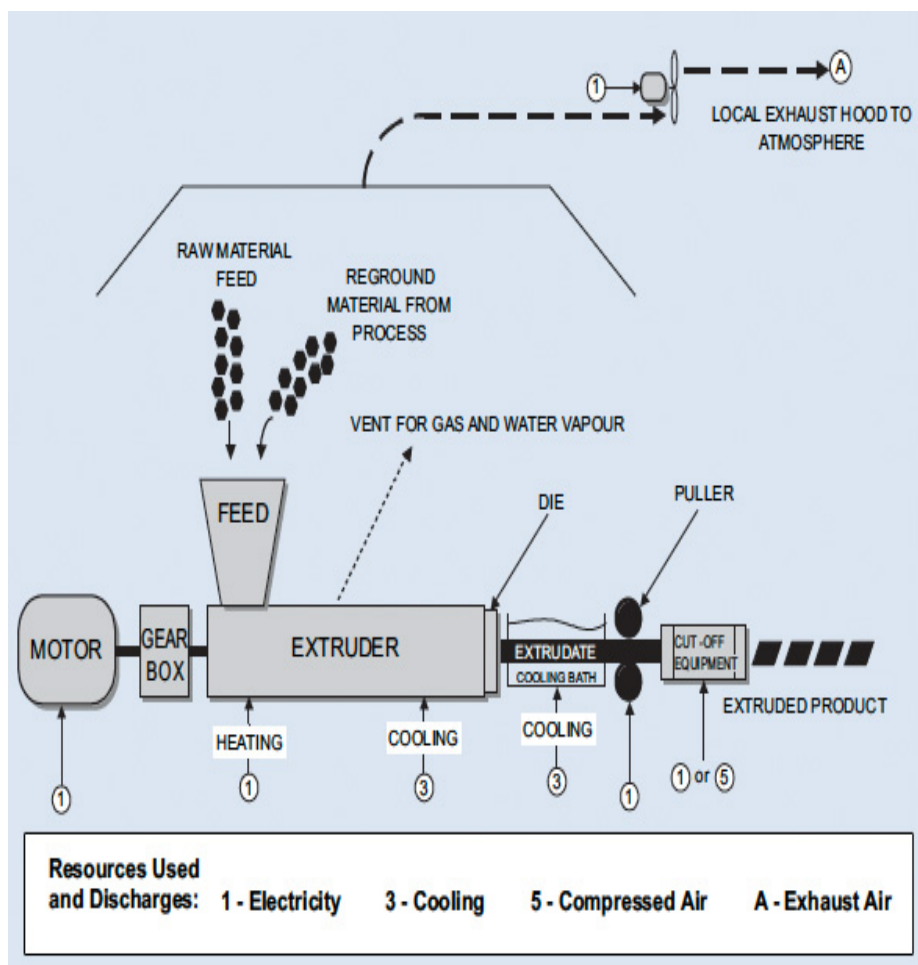

Fig 1: Extrusion process

As the mass passes through the extruder screen, the resulting extrudate eventually break under their own weight. Usually the extrudates have the same length. The extrudates must have enough plasticity in order to deform, but an excessive plasticity may lead to extrudates which stick to each other as they are collected and further processed in the spheronizer. The diameter of the segments and the final size of the spheroids depend on the diameter of the openings in the extruder screen. In order to obtain reproducible results, it is recommended to monitor extrusion parameters such as: feed rate, powder consumption, dies temperature and compression chamber pressure.

2.2 Spheronization
In the process of spheronization, formation of spherical particles from the extrudates produced by extrusion. The essential part of the spheronizer is the friction plate. The indentation patterns on the plate can have various designs, which correspond to specific purposes. The most common design is the cross-hatch pattern with grooves intersecting each other at 90° angles. In order to form spheroids, the extrudate are brought onto the rotating friction plate of the spheronizer, this imparts a rolling motion to the material.
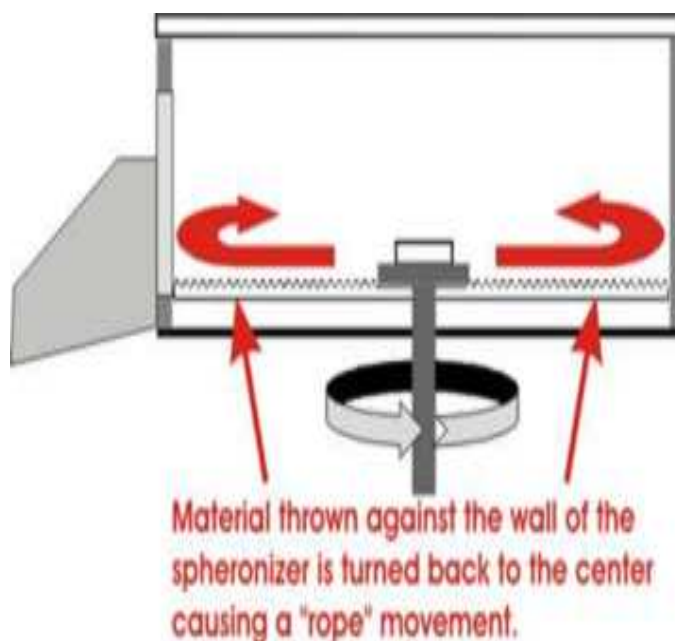

Fig 2: Spheronization process

Following the collisions between the extrudates with each other and with the friction plate and the stationary walls of the spheronization chamber, the cylindrical segments change their shape and size. The transition from the almost cylindrical segments to spheres during the spheronization process occurs in several stages. The resulting spherical shape of the pellets is correlated to the peripheral velocity of the plate. As the spheronization process begins, the processed material begins to move inside the spheronizer on at rajectory which resembles a woven rope. In addition, in order to obtain a high yield of spherical pellets, it is essential that the extrudates are non-friable and that they have suitable plastic properties which allow them to take a spherical shape.

The process of spheroid formation by extrusion-spheronization is similar to the wet granulation process, claiming the presence of a moistening liquid. However, there are two major differences in the granulation steps: the amount of granulation fluid required to obtained pellets with uniform size and sphericity is likely to be higher than for a similar wet Granulation uniform dispersion of the granulation fluid leads to a product with a good quality. Extrusion-spheronization is a versatile process for producing pellets with useful properties. However, the process is more labour intensive and more expensive than the conventional wet granulation technique, as its use should be limited only to the production of spherical pellets for controlled release of drugs. Technological advances now allow the production of spherical pellets by new processes, such as fluid-bed granulation and rotary granulation. In these cases, specialized equipments allow the whole cycle of wet spheronization, drying and coating of the pellets to be performed in one closed system [7].

Microcrystalline cellulose is the outstanding standard for preparation of pellets by extrusion and spheronization it provide unique characteristics of plasticity and cohesiveness of their wet masses [8-11].
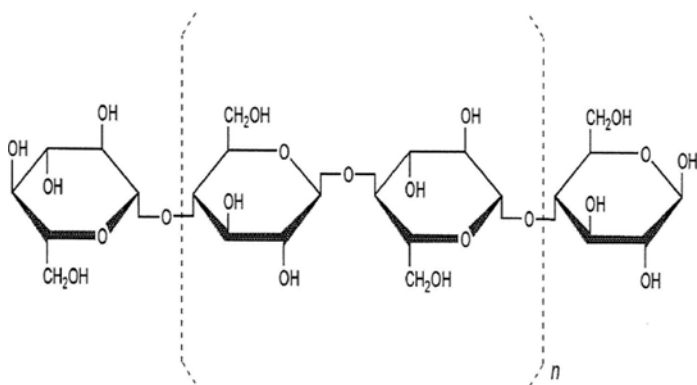

Fig 3: Microcrystalline cellulose

Two models have been proposed to explain the behavior of MCC during extrusion spheronization process:

I.   In the first model, MCC is described as a 'molecular sponge' [12]. The MCC particles are able to hold water in a manner like 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 spheronization. During the spheronization phase, the sponges are densified due to collisions between particles and the spheronizer plate and wall, and water facilitates spheronization of pellets.

II. 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 forma 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 spheronization becomes possible [13].

In spite of its excellent characteristics as an extrusion spheronization aid, in several cases MCC is not considered as the excipient of choice for the production of pellets via extrusion spheronization due to the following reasons:

➢ Drug adsorption onto the surface of MCC fibers has been reported [14].
➢ Several authors reported the chemical incompatibility of MCC with a number of drugs [15].
➢ An effect of MCC powders originating from different suppliers on pellet properties has been reported [16].
➢ A prolonged drug release was reported when using poorly soluble drugs in a mixture with MCC 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 [17].
➢ 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.

Alternative excipients for microcrystalline cellulose to obtain pellet disintegration and/or fast drug release from MCC-based pellets, several strategies have been reported (incorporation of water-soluble fillers, disintegrants, surface active agents and co-solvents). 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 [18]. A higher 2-propanol fraction in the granulation liquid improved pellet disintegration and increased drug dissolution due to less bonding between the particles [19]. However, this method also resulted in pellets with reduced mechanical strength.

3.   Ideal Properties Required In the Extrusion Spheronization Aids
1.   Water insolubility
2.   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
3.   Cohesiveness
4.   Sufficiently large surface area for interaction with water and the components of the formulation
5.   Ability to enhance the drug release [20, 21].

4. Alternatives to Microcrystalline cellulose
This article reviews several alternative extrusion spheronization aids such as powder cellulose, starches,

chitosan, pectinic acid, β-cyclodextrin (CD), sodium alginate, Polyethylene oxide and carrageenan.

4.1 Powder cellulose

Fig 4: Powder Cellulose

Powdered cellulose is produced from the same starting material like microcrystalline cellulose only one step missing that is partial hydrolysis. This retains a higher degree of polymerization and a lower crystallinity index compared to MCC. While MCC is hydrolysed reaching the level off degree of polymerization about 200– 350, the chains of powdered cellulose contain different crystalline and amorphous parts. Lindner and Kleinebudde prepared the pellets by using powdered cellulose and evaluated for some parameter, unlike to mcc it requires binder polymer in wet massing liquid pellets with 30% paracetamol was prepared. It was found that Pellets prepared with powdered cellulose had a higher porosity, less spherical compared to those prepared with MCC and dissolution is slightly faster [22]. When high concentration of powdered cellulose is used for pellets formulation, it found difficult because powdered cellulose requires more water for extrusion but it has low water holding capacity. Water movement occurs during extrusion due to which material is compressed inside extruder and extruder chocks. The material inside the extruder was compressed, resulting in a dry mass which blocked the extruder [23, 24]. Alvarez *et al*. compared powdered cellulose with MCC and included 25% and 50% furosemide as a model drug pellets produced with powdered cellulose found higher porosity, roughness, and friability size distribution is a broader only release of drug is faster [25].

Pellets produce using powder cellulose having higher porosity, roughness, slightly faster dissolution and less spherical as compare to microcrystalline cellulose.
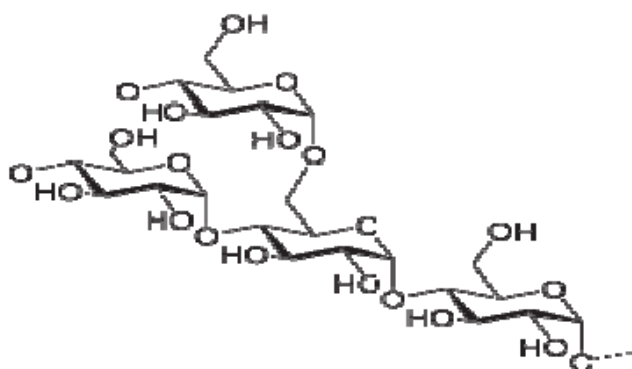
4.2 Starch

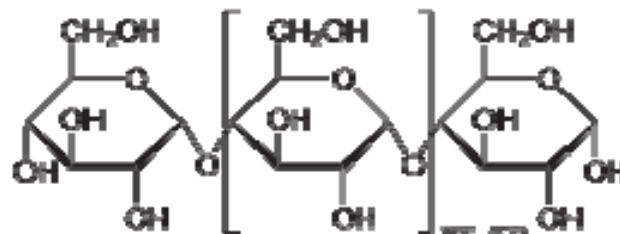
Fig 5: a) Amylopectin

Fig 5: b) Amylose

Almeida *et al*. might get spherical pellets using a combination of starch and dextrin [26]. Dukic *et al*. have used modified starch UNI-PURE®EX57 as substitute extrusion-spheronization aid with 25% of drug loading (theophylline). Addition of binder is essential for good sphericity Pellets. The obtained pellets were with constricted size distribution and high yield. Starch helps in rapid disintegration of the formulation [27, 28]. Dukic *et al*. 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 while MCC allowed only 40% containing formulation of the drug release in 75 minutes. In excess of 90% of piroxicam was released in 45 minutes from the starch-based formulation; in the case of MCC only 30% drug release was found in 45 minutes. Starch based pellets have quicker disintegration ability hence significant drug release difference was initiate in MCC and starch based pellets. Addition of sorbitol as a binder additional helped in the release of piroxicam from the formulation (more than 90% in 30 minutes) [29]. Otsuka *et al.* used a mixture of corn starch (27%, w/w), crystalline lactose (63%, w/w) and theophylline (10%, w/w) with HPC solution as binder. The resulting pellets showed good flow ability and mechanical strength. The authors determined that pellets made of starch and lactose were beneficial as raw materials for coated granules, but too tough for use as raw materials for tablet preparation, although they did not provide any data on morphological characterization or drug release [30]. Starch-based pellets were also gained by use of mixtures of 67.5% MCC and 30% native corn starch by Junnila *et al.* But, in this case, the high proportion of starch directed to defects in pellet shape and surface texture. Adding polysorbate 80 as a surface active agent somewhat improved wetting and shape, while the effect was not sufficient to produce fully round pellets. This group afterward proposed the use of waxy corn starch as a co-adjuvant for pellets produced by extrusion-spheronization [31, 32].

Pellets yield using starch helps in rapid disintegration of the formulation, good flowability and mechanical strength.

4.3 Chitosan

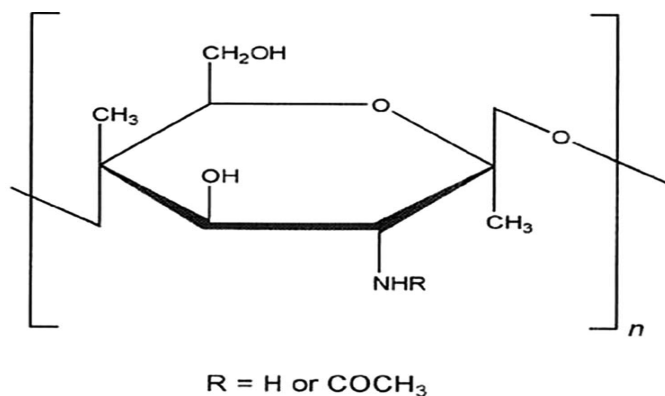**Fig 6:** a) Chitosan in powder form.

Fig 6: b) Chitosan

Goskonda and Upadrashta prepared pellets using a mixture of Avicel RC-591 (a spray-dried mixture of 89% MCC and 11% SCMC) and different grades of chitosan (20% of Seacure 142, 242, 342 or 442). Further viscous grades of chitosan produced pellets with rough surfaces and slower paracetamol release rate [33]. Tapia *et al.* showed that it was likely to produce similar pellets by adding a solution of chitosan dissolved in dilute acetic acid (as granulation liquid) to the powder mixture containing MCC. The resulting chitosan portion in the pellets was as low as 2-3% w/w. Diclofenac sodium release was significantly slower in formulations containing chitosan (i.e. approx. 100% in 6 h, rather than in 30 min) representing that effective drug release control can be achieved without the necessary for the pellets to be coated in polymer [34]. Santos *et al.* prepared pellets including chitosan (4 or 16%), MCC (50%), povidone, a filler excipient (lactose, tribasic calcium phosphate and β-CD) and diclofenac sodium as the model drug. an increase in the percentage of chitosan give rise to in a significant increase in the surface roughness and in fewer porous pellets. Pellets containing chitosan with suitable physical characteristics were obtained when an alcohol/water mixture 50% (v/v) was used, but in this situation effective control of drug release was not achieved [35]. Steckel and Mindermann-Nogly were able to produce pellets with mixtures of 30:70 to 50:50 of chitosan /MCC or 30:70 and pure chitosan and with demineralized water or diluted acetic acid as granulation liquid, respectively. Partial dissolution of chitosan with the suitable concentration of acetic acid made the wet mass extrudable, by increasing flexibility and cohesiveness. Powder mixtures containing high amounts of chitosan required higher concentrations of granulation liquid and acid to yield pellets with good morphological and mechanical properties. Increasing the acetic acid concentration up to 0.2 N give rises to a sticky extrudate or pellets with a rod-like appearance. But, no model drug was used in this study and therefore drug release rates were not evaluated [36]. Agrawal *et al.* to examine the use of chitosan in the manufacture of pellets without MMC but containing other excipients such as fine particle ethylcellulose (FP-EC) and HPMC, with caffeine as the model drug. Pellets with good mechanical properties were achieved with mixtures having FP-EC as the main excipient, 10-15% chitosan and 5-10% HPMC and water as the granulation liquid. Composition (% chitosan, % HPMC and water) and process variables (spheronizer and extruder speed) considerably affected the physical properties of pellets, but not drug release: caffeine was directly released from the pellets. Increasing the amount of chitosan in mixture produced smaller pellets of altered shape and yield [37, 38]. Jess and Steckel studied the effect of the degree of deacetylation of different grades of chitosan on the extrusion-spheronization method, with budesonide as the model drug and 0.2 N acetic acid solutions as granulating liquid. Variable rheological measurements designated that the degree of deacetylation affected the viscoelastic properties of the wet mass and enlarged the extrudability. The pellet properties (pellet size and shape, crushing strength and friability) enhanced with increasing deacetylation levels. Results specified that only chitosan with a degree of deacetylation >99% was suitable for extrusion/spheronization. The degree of deacetylation did not appear to have an excessive effect on drug release in these pellets and in all circumstances pseudo-zero order release kinetics were observed [39]. Charoenthai *et al.* have examined the impact 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 was influenced by the type and amount of chitosan, added sodium alginate, and dissolution media. Moreover, molecular weight of chitosan exhibited a major effect on the formation and characteristics of the obtained pellets and lower molecular weight chitosan had an improved pellet forming property [40]. Charoenthai *et al.* have investigated two types of different molecular weight chitosan as pelletization help in extrusion spheronization using water as a granulating liquid. The model drug used was paracetamol. The quantity of MCC necessary for the preparation of pellets was decreased with the aid of calcium salts (calcium salts decrease solubility of sodium alginate by ionic interaction). MCC might be completely removed from the formulation [41].

Pellets using chitosan are less porous, roughness and effective drug release rate control can be reached. Require higher concentration of granulation liquid and acid to produce good morphological and mechanical properties, Increses flexibility and cohesiveness.
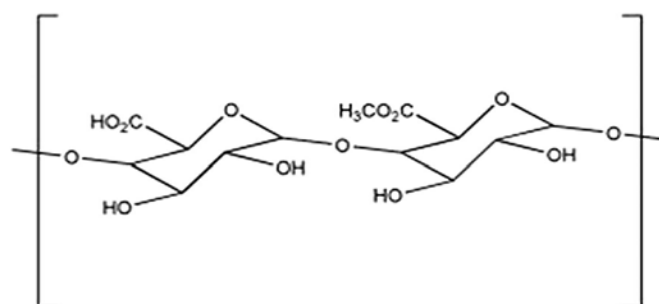
4.4 Pectinic acid

Fig 7: Pectinic acid.

Pectin is a partially water-soluble, gel-forming polysaccharide containing of polygalacturonic acid extracted from apple pomace or citrus peel. Different substitutions at C6 affect in the free acid, a methoxylated or amidated product. Also, the different pectin grades vary in their degree of methoxylation and amidation. Most pectin types are not appropriate as pelletisation aid if processed with pure water as wet massing liquid because of the high degree of swelling and the stickiness of the extrudates [42]. However, the addition of additives like ethanol, calcium chloride or citric acid might increase the result of the pelletisation process dependent on the pectin type [43]. This was recognized to the lower solubility of pectin in the existence of these additives. The effect of the different additives was concentration dependent. It was likely to find

quantum chemical descriptors to explain the outcome of the additives in the wet massing liquid: the two most significant factors being a small molecular size and a strong hydrogen bond forming ability of the additive [44]. The cross-linking of amidated low-methoxylated pectin with calcium ions was analysed additional. Due to cross-linking the calcium ions were capable to reduce the solubility and swelling of pectin through pelletisation, which caused in more spherical pellets. Though, the incorporation of additives itself is a severe disadvantage 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 effectively pelletised in combination with lactose and 1% riboflavin as a model drug using water for pelletisation [45]. The resulting pellets remained not perfectly round, but the spheronization phase was not optimised. The pellets were mechanically stable and partly disintegrated throughout dissolution experiments. The release of riboflavin was satisfactory. In a further study the drug load was varied from 1% to 80% [46]. Pectinic acid had a high drug loading capacity and created disintegrating pellets that are well matched for fast delivery of drugs through a low water-solubility. The pellets were also mechanically stable. Though, pectinic acid is more to sensitive type and amount of drug and is, therefore, not as universally applicable as the conventionally used MCC [47]. Sriamornsak et al. prepared pellets having theophylline with mixtures of MCC and calcium acetate and HPMC solutions as granulating agents. An insoluble coating of calcium pectinate was found by interfacial complexation, by soaking the pellets in an aqueous solution of pectin [48].

Produced disintegrating pellets for the fast delivery of the drugs, mechanically stable pellets with high drug loading capacity
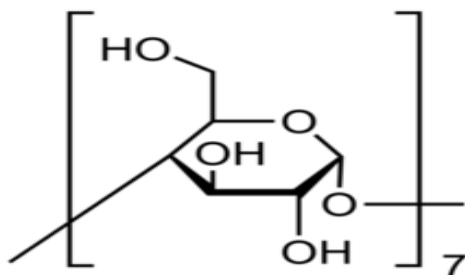
4.5 B Cyclodextrin

Fig 8: β Cyclodextrin

Gazzaniga et al. stated the use of the cyclic oligosaccharide β-cyclodextrin (β-CD) as a pelletizing agent in the extrusion-spheronization process. Pellets with suitable physical characteristics were prepared with drug/β-CD mixtures with MCC contents below 20%. However, it was not possible to obtain pellets without MCC because of the poor quality of extrudates of β-CD while using water as a wetting agent [49]. The result of cyclodextrins on drug release from pellets has also been studied by Debunne et al. In this study, the impact of hydrophilic excipients on the in vitro drug release from MCC based pellets was examined. The use of cyclodextrins (β-CD or hydroxypropyl-β-CD), in a proportion of 20%, in pellets based on Avicel PH 101 improved the release of piroxicam. As estimated, the influence of the less soluble β-CD on the dissolution rate was lower than that of hydroxypropyl-β-CD. Though, release from pellets containing hydroxypropyl-β-CD

was comparable to that from pellets based on a mixture of Avicel PH 101 and CL 611 (MCC co-processed blend containing SCMC) [50]. Santos et al. used 16% β-CD in mixtures of MCC/chitosan or MCC/ xanthan gum. Pellets formed by the MCC/xanthan gum/β-CD mixture exhibited immediate release of the model drug diclofenac sodium. The release manners of tablets made of pellets comprising β-CD was irregular, with diffusional exponent (n) values of 0.625, representing that drug diffusion and erosion were conflicting mechanisms of drug release from those tablets [51, 52]. Bon et al. proposed the use of a cyclodextrin-based polymer (highly cross-linked cyclodextrin-based polyester) as a pelletizing aid to accelerate the release of poorly soluble drugs from pellets gained by extrusion-spheronization. These authors compared the performance of pellets prepared with mixtures of MCC/natural β-CD or MCC/cross-linked β-CD-based polymer, with nimesulide as a poorly soluble model drug. Pellets that were explained with cross-linked β-CD-based polymer disintegrated completely, therefore accelerating dissolution of nimesulide (75 ± 2% in 120 min vs. 12 ± 1% for pellets with only MCC). Pellets containing the equivalent amount of β-CD did not disintegrate and the dissolution was considerable lower (35 ± 1% after120 min). This is another example of how the combination of high water soluble substances is not sufficient to produce the disintegration of pellets with MCC, but needs other excipients with high water holding capacity and swelling [53]. CD, with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large diversity of guest molecules to form non covalent inclusion complex. Chemically they are cyclic oligosaccharides and existing as α-, β-, and γ-CD. The cavity size of α-CD is inadequate for many drugs and γ-CD is expensive. B-Cd were extensively used in the early periods of pharmaceutical applications because of its ready availability and cavity size suitable for the extensive range of drugs. But the low aqueous solubility and nephrotoxicity restricted the use of β-CD especially in parenteral drug delivery [54, 55]. Villar-López et al. have established the preparation of pellets with 95% β-CD and 5% triamcinolone acetonide. The pellets had sizes and circularity comparable to those formulated with MCC. The pellets exhibited very fast disintegration. Additional coating over the pellets could be accomplished easily by the scientists [56]. Gainotti et al. 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 wherever high amount of β-CD is essential [57].

B-cyclodextrin helps to accelerate the release of poorly soluble drug
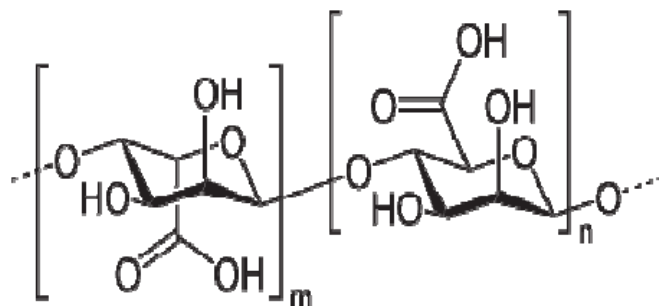
4.6 Sodium Alginate

Fig 9: a) Alginic Acid

Fig 9: b) Sodium alginate powder form

Fig 10: b) Polyethylene oxide powder form

Alginates, a set of anionic polysaccharides, are linear polysaccharides extracted from brown seaweed. They have varying amounts of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. The residues could vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. The homo polymeric states of M and G blocks are spread with regions of alternating structure (MG blocks) [58]. The composition and amount of the sequences and the molecular weight regulate the physical properties of the alginates. One of the most significant and useful properties of alginates is the capability to form gels in the presence of some multivalent metal ions such as calcium. The controlled accumulation of these ions technically leads to insoluble alginate gel formation. The affinity of alginates for calcium ions and their gel-forming properties is mostly associated to the overall fraction of G residues, the molecular weight of the polymer, and the calcium ion concentration at the time of gelation. While two G residues are adjacent in the polymer, they form a binding site for calcium. Alginates are of pharmaceutical concern because of their nontoxicity, biodegradability, and biocompatibility [59]. Sriamornsak *et al*. have prepared pellets having 30% (w/w) of sodium alginate. The adding of calcium chloride to the granulation liquid condensed swellability of sodium alginate and therefore allowed successful spheronization process [60]. Sriamornsak *et al*. have studied the result of the amount and type of calcium salts on the quality of pellets prepared using sodium alginate. Maximum of the produced pellets were of adequate quality. Addition of calcium acetate in the formulations slightly improved the drug release. A more marked effect on increased drug release was understood when the calcium amount was increased. Combination of calcium carbonate, however, revealed a lesser marked effect. Sodium alginate does not achieve all the properties of the ideal extrusion spheronization aid. The pellets might not be prepared without the aid of MCC. Although the quantity of MCC required for the preparation of pellets was reduced with the aid of calcium salts (calcium salts reduce solubility of sodium alginate by ionic interaction), MCC could be totally removed from the formulation [61].
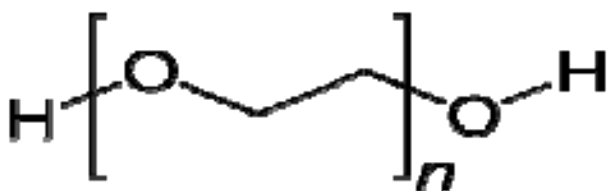
4.7 Polyethylene Oxide

Fig 10: a) Polyethylene oxide

The USP 29 defines polyethylene oxide (PEO) as a nonionic homo polymer of ethylene oxide, characterized 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. It is highly water soluble with recognized binding properties that is usually regarded as safe for use in solid oral human dosage forms. PEO has been used in the preparation of buccal tablets in mixture with Carbopol® for the preparation of sustained release tablets, for the production of nanoparticles, and for the development of pulsatile delivery systems [62-65]. PEO shows binding prop b rties in both the wetted mass and the extrudates, but after spheronization the product was between accurate spheres and small extrudates, hence it could be measured as a good extrusion aid but not a spheronization aid. These properties directed to the use of plasticizers so as to increase the sphericity of the product. Chien and Nuessle recommended 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 expected that this structural similarity would permitPEG400 in the wetted mass to similarly act as a plasticizer during the extrusion and spheronization steps. Theoretically, with the applied forces of extrusion, PEG400 would be accomplished of moving between the strands of PEO to be stated to the surface. Then, at the surface, the waxy texture of PEG400 would act as an adjunct lubricant to water to decrease surface extrudate destruction and dehydration. Methoxypolyethylene glycol was recognized as a potential plasticizer analogous in chemical structure to PEG400 but less chemically reactive because of the methoxy end group [66]. Effective 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 exposed 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 mixture can be efficiently 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 necessary, and MCC cannot be used because of its chemical incompatibility and release retarding property [67]. Rama *et al*. have established 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. Every of the batches in this study formed beads that

were highly spherical regardless of the formulation and process variables, signifying that coarse ethylcellulose is a good excipient for the production of beads by extrusion-spheronization. These beads show the necessary physical and mechanical characteristics for further pharmaceutical processing such as capsule filling and coating [68].
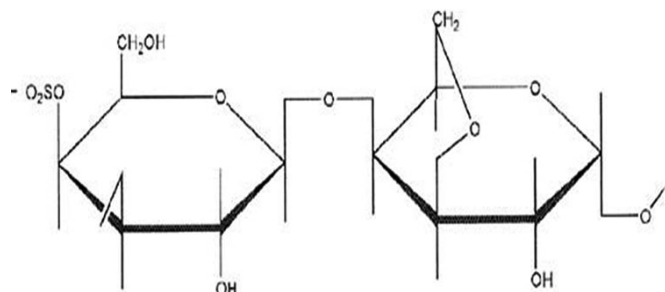
4.8 Carrageenan

Fig 11: a) Carrageenan.

Fig 11: b) Carrageenan powder form.

Carrageenan was used in the extrusion-spheronization process by Garcia and Ghaly to yield bioadhesive pellets. Kappa carrageenan was involved (10 to 30%) in pellets containing MCC and co-processed MCC having 11% SCMC, with water as the granulating agent. Pellets of between 1.16 and 1.69 mm *In vitro* bioadhesion and glipizide release from bioadhesive pellets was affected by the level of carrageenan and the existence of SCMC. As the proportion of carrageenan increased, drug release decreased and bioadhesion increased. Bioadhesion was increased through carrageenan and SCMC content [69]. Bornhöft *et al.* studied three varieties of carrageenan, iota-, kappa- and lambda-carrageenan, with the aim of obtaining an appropriate alternative to MCC and used α-lactose monohydrate as filler. Iota- and lambda-carrageenans give rise to extrudates that might not be spheronized and kappa-carrageenan produced extrudates with suitable plastic and brittle properties for the spheronization process. A least of 5% of kappa-carageenan was essential to produce pellets without MCC. An increase in the range of optimum water content enhanced the robustness of the pelletizing process, but binding more water might lead to stability problems with sensitive drugs [70]. Thommes and Kleinebudde yield pellets containing 20% of kappa-carrageenan with different fillers (lactose, mannitol, maize starch and dicalciumphosphate dehydrate) and drugs (acetaminophen, theophylline, mesalamine and hydrochlorothiazide). Results indicated that most pellets remained of acceptable quality regarding size, size distribution and shape. The effects of different fillers on the pelletization process and the pellet properties were insignificant. In compare to MCC pellets, drug release from

kappa-carrageenan pellets was considerably less affected by the solubility of the drug. Pellets containing kappa-carrageenan disintegrated in less than 10 min. Regardless of the filler used, the release was completed within less than 20 min [71, 72]. It was likely to produce round pellets in the whole ratio range of κ -carrageenan but 10% was established to be the most adequate. The range of optimal water content was from 46% to 61% for carrageenan while only from 32% to 36% for MCC. Carrageenan pellets were analogous 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 spheroniser [73, 74]. Thommes and Kleinebudde have equated different types of carrageenans from different suppliers: one ι-, five κ -, and one λ- carrageenan. Four of the five tested κ - carrageenans caused in pellets with acceptable shapes, sizes, and size distributions using a high drug load of 80% hydrochlorothiazide. These pellets have related properties over an extensive range of water contents ranging from 90% to 105%. [75] The properties of j-carrageenan-built pellets were affected by the drying conditions of the pellets as well as by the existence of cations in low concentrations [75].

Conclusion
Several polymer studied are suitable for preparation of pellets, some of them allows to overcome some disadvantages of MCC. Some of the polymer discussed forms pellets in combination with MCC or require some plasticizer/lubricant/binder to form good quality of pellets. In addition, the true potential of some of the materials evaluated as extrusion-spheronization aids is difficult to assess based on the available information, since data on essential characteristics are missing like no dissolution profiles available as no drug was incorporated in the formulations, maximal drug load not determined. None of the polymer studied proven that much of robustness in formulation of pellets likes MCC.

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