Non-MCC materials as extrusion-spheronization aids in pellets production

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Microcrystalline cellulose (MCC) is the most widely used base excipient for pellet formulations, mainly because it provides wet masses with appropriate rheological properties for extrusion-spheronization. However, MCC has certain limitations that hinder its universal use in extrusion-spheronization, namely the fact that pellets do not disintegrate after releasing the drug and pellets do not efficiently control the release of highly hydrophilic 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. The use of other cellulosic materials and natural excipients, such as saccharides, oligosaccharides, starch, alginate, chitosan, pectinic acid or carrageenans, or synthetic polymers, mainly polyacrylates and polyvinylpyrrolidone, is revisited and their effects on the properties of the final pellets are discussed. The approaches applied to produce the pellets and their ability to regulate drug delivery are also illustrated.

Key words: Pelletization - Extrusion - Spheronization - Pellet - Cellulose - Saccharides - Polysaccharides - Polyacrylates - Drug delivery.

I. INTRODUCTION

1970, the use of pellets as multiparticulate delivery systems has become widespread and, in recent years, increasingly important in view of the numerous technological and biopharmaceutical advantages over traditional monolithic forms. Extrusion-spheronization is commonly used in the pharmaceutical industry to produce uniformly sized pellets. This technique is especially useful for making dense granules for controlled-release solid oral dosage forms of pellets containing minimal amounts of excipients. Pellets produced by extrusion-spheronization have an intrinsic tendency towards slow release of the active ingredients [3-5]. This is influenced by factors including shape [6], quantity and nature of the granulation liquid [7], and of course the excipients used to aid extrusion-spheronization. Microcrystalline cellulose (MCC) is the most widely used base excipient for pellet formulations [8-11], mainly because wetted MCC powder masses provide mixtures with appropriate rheological properties for extrusion-spheronization [12]. If large amounts of MCC are replaced by another component, the rheological properties typically become much more dependent on the precise amount of water added, thus complicating the production process, and in particular making it more difficult to control the final size and shape of the pellets. Despite the excellent characteristics of MCC, the reluctance of MCC-based pellets to disintegrate even when mixed with disintegrating agents, though convenient for the preparation of sustained-release formulations, hinders exploitation of the advantages of pellets when fast release of drugs with poor solubility in aqueous media is desired [13-17]. Other disadvantages that hamper the use of these pellets include drug-excipient incompatibility, and the adsorption of drugs on to the surface of MCC fibers [10]. Therefore, it is usually necessary to add other excipients in order to improve the extrusion-spheronization processes and further drug release.

In recent years, we have mainly focused our research activity on improving the performance of MCC pellets and searching for alternative excipients to MCC. There have also been attempts to develop more effective techniques for morphological characterization of pellets [18-20].

Various review articles on extrusion-spheronization processes for pellet production have been published, although in different languages [11, 21-26]. Recently, Dukić-Ott *et al.* [10] published an excellent, thorough critical review of the approaches carried out by different researchers to totally replace MCC with other materials in order to avoid the disadvantages of MCC and provide a broad application platform for extrusion-spheronization. The aim of the present review is to report and discuss the different alternative materials that can be used to partially or totally replace MCC in order to improve the properties and the quality of pellets produced by the extrusion-spheronization technique. The review is divided into three parts: in the first part we briefly discuss the use of cellulose and cellulose derivatives in extrusion-spheronization processes; in the second part we deal with natural excipients (saccharides, polysaccharides, alginates and others) used in pelletization, and their effect on the properties of the final pellets, and in the final part we discuss the different approaches that have been used to produce pellets from synthetic materials.

Celluloses in extrusion-spheronization processes

Cellulose is the most abundant naturally occurring biopolymer and consists of long chains of anhydro-D-glucopyranose units. Cellulose is insoluble in water and in most common solvents; the poor solubility is primarily attributed to the intra- and intermolecular hydrogen bonding between chains [27]. Celluloses are used in various pharmaceutical and biomedical applications and the transformation or derivatization of cellulosic material has widened the applications still further. Typical treatments of cellulose include micronization, partial depolymerization by treatment with mineral acids and modifications such as esterification and etherification at the hydroxyl groups.

Purified microcrystalline cellulose is partially depolymerized cellulose, prepared by treating α-cellulose with mineral acids and typically with a degree of polymerization of less than 400 [28]. When cellulose reacts with acid, the β(1-4) glycoside bond is attacked and the acetal linkage is broken, resulting in hydrolysis of the chain and a decrease in the degree of polymerization. Since its introduction in the 1960s, MCC has provided great advantages in the formulation of solid dosage forms and despite some characteristics that limit its application (relatively low bulk density, moderate flowability, loss of compactability after wet granulation and sensitivity to lubricants),

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MCC (particularly the commercial grade, Avicel PH-101) remains the major excipient used in the preparation of pellets by extrusion/spheronization.

MCC is reported to aid the extrusion-spheronization process by absorbing and retaining a large quantity of water, binding and lubricating the powder material, improving moistened wetted mass plasticity and enhancing rheological properties [12]. The interactions between water and MCC are therefore essential features and responsible for producing spherical pellets with a smooth surface, low friability and low density. Various studies have explored the ability of MCC to "catch" water in their structure [29, 30] and two theories have even been proposed to explain this interaction that is so important for the extrusion-spheronization process: the "molecular sponge model" [30] and the "crystallite-gel model" [31]. Regardless of these models and unlike other excipients, MCC has the advantage and peculiarity of being granulated by the addition of water, to produce pellets of acceptable quality.

To date, MCC has been used in several studies as the main excipient for pellet preparation. In many such studies, MCC is used as the only aid to extrusion-spheronization, although many other materials have been introduced to improve the properties of pellets. Different types of cellulosic material are often used to produce the best results. Over the years, various cellulose derivatives have been proposed as alternatives to MCC, including diverse grades of Avicel (PH-101, PH-102, PH-103, PH-105, RC-501, RC-581, RC-591, CL-611, 955), Emocel and Unimac (MG-100, MG-200) and silicified microcrystalline celluloses (Prosolv). Some examples of different grades of microcrystalline cellulose and powdered cellulose commonly used to prepare pellets are shown in *Table I*.

As mentioned above, there are certain disadvantages associated with the use of MCC as the only extrusion-spheronization aid. Although one of the claimed advantages of MCC is the possibility of producing pellets with high drug loading [2], this is not feasible for all drugs [32]. Different approaches have been used in order to predict the maximum drug loading in pellets. For example, Jover *et al.* [33] evaluated an experimental grade of microcrystalline cellulose (Avicel 955) containing 5 % of methylcellulose (MC) as an aid to producing pellets with high drug loading (80 %) by extrusion-spheronization. These authors tested twenty model drugs and concluded that although some factors required further investigation, production of spherical pellets with high drug loading is possible with Avicel 955. Podczeck *et al.* [34, 35] proposed the use of modified MCC based on the "wet cake" associated with the manufacture of Avicel PH and RC grades, which contain different levels (6 or 8 %) of a cellulose derivative, sodium carboxymethylcellulose (SCMC). The new types of MCC were able to form good quality pellets with three model drugs with

Table I - MCC and cellulose microfine grades most commonly used in pelletizing by extrusion spheronization.

Cellulose	Trade name	Grade	Particle size (µm)	Moisture (%)	Bulk density (g/cc)	Degree of crystallinity (%)	Carr index	Ref.
MCC	Avicel	pH101	76.5	4.65	0.313	68.6	27.5	[17, 124, 155-162]
	Avicel	pH102	132.8	4.18	0.309	74.6	26.6	[124, 155, 157, 163]
	Avicel	pH103	501	>3.0	0.26-0.31		25.2	[52, 169]
	Avicel	pH105	201, 19.9	>5.0	0.20-0.30	68.1	31.5	[157, 169, 171]
	Avicel	pH112	1001	>1.5	0.28-0.34			[159, 169]
	Avicel	pH200	1801, 144.3	2.0-5.0	0.29-0.36	67.5		[157, 163, 169]
	Avicel	pH301	73.6,52.9	4.03	0.430	76.4	23.4	[155-157]
	Avicel	pH302	136.4[1]	4.03	0.456		22.8	[155, 156, 159]
	Emocel	50M	70.9	4.29	0.270		28.4	[155]
	Microcel	MC101	99	-	-		24.5	[164,172]
	Microcel	3E200	-	-				[164]
	Ceolus	KG801	66.7	4.26	0.194		34.7	[155]
	Celex	101	57.2	3.92	0.282		29.0	[155]
	Pharmacel	101	62.2	4.63	0.304		30.6	[155]
	Pharmacel	102	143.2	4.24	0.335		24.0	[155]
	Celex	101	57.2	3.92	0.282		29.0	[155]
	Vivapur	101	68.0	4.63	0.315		29.53	[155]
	Unimac	MG100	39-39.9	3.7-7.15	0.324		20.6,42.02	[52, 170,171]
	Celpac1	50	60					[165]
MCC with methylcel-lulose	Avicel	955 (5 %[2])	-	-	-			[33, 173]
Silicified MCC	Prosolv	50M	81.4	4.29	0.301		25.9	[155]
	Prosolv	SMCC50	41,57					[157, 158]
MCC with SCMC	Avicel	RC501 (8.5 %[3]) Bulk Dried				30[4]		[52]
	Avicel	RC581(11 %[3]) Bulk Dried				70[4]		[52, 166]
	Avicel	RC591 (11 %3) CoSpray-Dried	34.8	3-5	0.28-0.33	70[4]		[52, 157]
	Avicel	Cl611(15 %3) CoSpray-Dried	50*	<3	0.34-0.42	70[4]		[52, 166]
Powdered cellulose	Elcema	P050 (Powder)	30.7	5.76 %	0.25	35.8		[157]
	Elcema	P100 (Powder)	50.5	4.24 %		44.3		[37, 157, 167, 168]
	Elcema	F150 (Fribrous)	50.1					[157]
	Elcema	G250 (Granular)	108					[37, 157]

[1]Nominal particle size. [2]% methylcellulose. [3]% SCMC. [4]% colloidal.

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low (ibuprofen), intermediate (lactose) and high (ascorbic acid) water solubility, whereas Avicel PH101 could not form pellets with the same level of ibuprofen. The cause of the failure of standard MCC to produce pellets with high level of ibuprofen was the insufficient rigidity of the mixtures during the extrusion-spheronization process. The presence of poor water soluble substances in high proportion significantly reduced the ability of MCC to hold and retain water and subsequently, promoting the water migration in the mass during the process, decreasing its cohesiveness and resulting in the formation of less rigid systems. Inclusion of low percentages of the cellulose derivatives SCMC or MC improved the hold water capacity of the mixtures increasing the restriction of migration of water. In consequence, the cohesiveness increased providing more rigid systems that facilitated the formation of pellets with high drug content. The inclusion of other pharmaceutical excipients with high capacity to retain water could also probably improve the extrusion-spheronization behavior of standard MCC in the presence of a high proportion of hydrophobic substances.

Binding agents have been also proposed to produce better MCC pellets with low and medium drug content. Law and Deasy [36] studied spray-drying and physical mixtures of MCC and HPMC, HPC, SCMC and polyvinylpyrrolidone (PVP) as extrusion-spheronization aids. By including lactose (20 %) in the formulations, these authors found that spray-dried combined excipients produced pellets with higher yield, better sphericity and improved tolerance to minor variations in the level of water added than in the physical mix excipient. The authors concluded that mixtures containing HPC and PVP were the most satisfactory of the hydrophilic polymers examined, because they had the least adhesive strength, thus, favoring maximum yield of highly spherical pellets.

Another disadvantage associated with the use of MCC is that drug release from MCC based pellets is generally slow, particularly for drugs with low water solubility [17]. This has mainly been attributed to the low porosity of pellets due to contraction during the drying process [37]. To overcome this, various authors have proposed substituting MCC with powdered cellulose (PC) [38, 39]. Lindner and Kleinebudde [38] observed that the rate of release of Paracetamol is markedly higher from extruded-spheronized pellets based on PC than from those based on MCC. However, PC displayed deficient mechanical properties and binding agents had to be incorporated in order to produce pellets. Alvarez *et al*. [39] evaluated the utility of PC as an excipient in pellets, with furosemide as a poorly water soluble and highly cohesive drug model. PC-based pellets prepared with 25 or 50 % furosemide showed a markedly higher release rate than MCC-based pellets, which may be attributable to the higher micropore volume of the former. The use of water as the granulating liquid produced smaller pellets with a wider particle size distribution, similar sphericity, greater surface roughness and higher friability than equivalent pellets prepared with MCC. The same research group [40] used PC-based pellets containing polyvinylpyrrolidone coated with a pH sensitive hydrogel obtained by an in situ photopolymerization-coating technique. For this purpose, PC-based pellets containing theophylline were prepared by extrusion-spheronization, sprayed with a solution of the monomers in ethanol:water (50:50 v/v), the cross-linker (N,N0-methylenebis (acrylamide) and an initiator (Irgacure_2959) and irradiated at 366 nm. The authors suggested that with a molar ratio of acrylic acid:lauryl acrylate of 88:12, the coating did not significantly change the shape, size or friability of the pellets, but considerably modified the theophylline release profiles.

Generally, the effect of MCC after wet granulation and drying is a contraction and a loss of compactability that yields no disintegrable pellets with low porosity. The inclusion of soluble substances, even in high proportions, is not normally able to produce disintegrable pellets. The presence of high soluble excipients increases the pellet porosity due to their dissolution during the release process but these substances are unable to break and destroy the tridimensional structure

formed by the MCC. The influence of the increase of pellet porosity over the drug release rate is directly related to the nature of the drug. Nevertheless, the addition of hydrophilic polymers able to swell and form viscous gel and tridimensional networks are capable of modifying the water holding capacity, contraction and compactability of MCC blends and, in summary, producing modifications in pellet structure during swelling by enhancing the release of drugs. These modifications are more effective when co-processed MCC blends, including hydrophilic polymers (i.e. SCMC) are used.

With this in mind, Chatlapalli *et al*. [41] used two cellulose derivatives, hydroxypropylmethyl cellulose (HPMC) or hydroxyethyl cellulose (HEC) wetted with isopropyl alcohol to manufacture pellets. HPMC and MCC produced pellets with the most desirable attributes, whereas HEC rendered pellets of lower sphericity and with rougher irregular surfaces. With water as the release medium, the HPMC-based pellets swelled to form a single viscous gel matrix that dissolved slowly, whereas HEC-based pellets were swollen but intact and eroded slowly. Kleinebudde [37,42] used hydroxypropyl cellulose of low substitution grade (L-HPC) in different mixtures with MCC. The pellets swelled in water media and did not disintegrate during swelling and dissolution. These authors also showed that the swelling process can almost be suppressed when freeze-drying is used to dry the pellets. The use of propyphenazone, caffeine and acetaminophen as model drugs also revealed that drug release was enhanced in the presence of L-HPC and drying pellets by freeze-drying led to an increase in drug release rate relative to that associated with the fluid-bed-drying process. In general, the process used to dry pellets has an important effect on the drug release rate. Several authors have reported that drying pellets by freeze-drying results in systems with a faster rate of drug release. Lutchman *et al*. [43] prepared pellets from mixtures of MCC and HPMC of different viscosity and used *in vitro* dissolution studies to show that the drug release rate could be improved by using different drying techniques, in the following order of increasing success: oven-drying, vacuum-drying, fluid bed-drying and freeze-drying. Similar results were obtained by Murray *et al*. [44], Song *et al*. [45] and Gómez-Carracedo *et al*. [46] with pellets of different compositions. Debunne *et al*. [47] evaluated the influence of several excipients on the *in vitro* drug release for MCC-based pellets prepared by extrusion-spheronization. The addition of sodium croscarmellose (Ac-Di-Sol) did not influence piroxicam release from MCC- based pellets. Nevertheless sodium carboxymethyl cellulose on its own or as a co-processed blend with microcrystalline cellulose (Avicel RC 581 and CL 611) enhanced the release of piroxicam (30 % release in 45 min for pure Avicel PH 101 compared with 95 % released in combination of Avicel PH 101 and CL 611 at a ratio of 1:3).

Sodium croscaramellose was also used by Souto *et al*. [14] and compared with sodium starch glycolate as superdisintegrant, in order to increase the dissolution rate of poorly water-soluble drugs, with hydrochlorothiazide as the model drug and water or water/ethanol as the granulating agent. Pellet morphology was not affected by the inclusion of SCMC. Nevertheless, the pellets did not disintegrate and SCMC afforded only a modest increase in the drug dissolution rate, attributable to the observed increase in pellet micropore volume.

II. OTHER POLYMERS OF NATURAL ORIGIN
1. Saccharides and oligosaccharides

Lactose, which is a disaccharide, is the most common filler and excipient used in the production of MCC pellets by extrusion-spheronization. Numerous studies have incorporated lactose as a filler, bulk material, soluble excipient or model drug in mixtures with MCC and/or other materials [15, 35, 48-51]. It has been reported that it is possible to produce round pellets with a narrow size distribution by incorporating this disaccharide in AVICEL PH101, even when lactose is included in high proportions (80 %) [49]. Podczeck *et al*. [34] also demonstrated the ability of some modified MCCs, containing 6 or 8 %

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SCMC, to form spherical pellets with 80 % lactose. Nevertheless, other varieties of MCC behave differently: Newton *et al*. [52] showed that mixtures of colloidal grades of Avicel (RC 501, 581, 591 and CL 611) with lactose produced pellets that were "rounded" rather than "round", principally due to the differences in the rheological characteristics of wet masses prepared from these colloidal grades of Avicel mixed with lactose [52, 53]. Basically, these colloidal grades of Avicel are co-processed blends of MCC containing 8.5 % (RC 501) 11 % (RC 581 and 591) of 15 % (CL grade) of SCMC with a colloidal proportion of 30 % or 70 % of RC 501. The highest proportion of SCMC and especially the colloidal content of these MCC grades affects their elastic behavior producing wet mixtures that show deficient strain properties during the spheronization steps. This behavior is common to pellets made with other excipients (i.e. starches) that incorporate hydrophilic macromolecules able to hold water and swell, as shown in the starches section.

Monosaccharides such as glucose, mannitol and sorbitol have also been used as active material [54, 55], soluble drug models and fillers [33, 56-58] in mixtures with MCC to prepare pellets, principally in order to analyze the influence of the solubility of the drug and the filler on the physical characteristics of pellets prepared by extrusion/spheronization. Including soluble saccharides in pellet formulations generally lowers the optimal water level required for the extrusion-spheronization process. The inclusion of sorbitol in starch-based pellets provided a wetter mass consistency and pellet yield [59, 60]. The presence of sorbitol also improved the surface morphology of dried pellets.

Gazzaniga *et al*. [61] reported the use of the cyclic oligosaccharide β-cyclodextrin (β-CD) as a pelletizing agent in the extrusion-spheronization process. Pellets with satisfactory physical characteristics were prepared with drug/β-CD mixtures with MCC contents below 20 %. Nevertheless, it was not possible to obtain pellets without MCC because of the poor quality of extrudates of β-CD when using water as a wetting agent. No model drug was used in the study and pellet morphology was only estimated on the basis of a visual inspection. Pellets containing triamcinolone acetonide (5 %) were prepared with microcrystalline cellulose (MCC) and/or a hydrophilic excipient (lactose, SCMC or β-CD) [15, 62]. Mixtures of MCC and β-CD (80 % to 93 % β-CD) produced pellets with higher yield and good size and shape. It was also possible to obtain spherical β-cyclodextrin pellets in the absence of MCC, although a kneading process was necessary in the presence of water and with partial evaporation of the solvent to produce an extrudable wetted mass. Inclusion of this cyclic oligosaccharide took place and as in the case of saccharides, lowered the optimal water level required for the extrusion-spheronization process. Torque-rheometry analysis used to characterize wetted masses prior to extrusion-spheronization showed that the amount of water needed to obtain maximum torque values in β-CD masses (0.16-0.18 mL/g, *Figure 1*) are much lower than those of the MCC (1.2-1.4 mL/g) and the consistency values were much higher for MCC masses than for β-CD mixtures. The amount of water required to produce maximum torque values in β-CD masses was independent of the rate of incorporation of water. However, the consistency depended mainly on the mixer used. We also found that higher consistency values and lower water requirements for moisturizing were obtained with a double sigma mixer than with other types of mixers such as an orbital mixer. Consequently, for the same amount of wetting agent added, pellets may or may not be obtained, depending on the granulating or kneading conditions. In this study, it was found that the inclusion of poorly soluble or sparingly soluble drugs in water such as triamcinolone acetonide or diclofenac sodium in β-CD mixtures significantly increased the consistency of wetted mixtures. Basically, these drugs may act as binder agents thus improving mass behavior and increasing extrudability. Furthermore, triamcinolone acetonide loaded pellets prepared with 95 % β-CD and no MCC [15] were of similar size and circularity to those formulated with MCC alone. Increasing β-CD content in pellets produced a reduction in size and a further increase in drug release. On the other hand, pellets prepared by β-CD or mixtures with less than 5 % MMC (93:2, β-CD:MCC) disintegrated quickly in dissolution medium, releasing 100 % of the poorly water soluble drug triamcinolone acetonide in less than 20 or 60 min, respectively (see *Figure 2*).

The effect of cyclodextrins on drug release from pellets has also been investigated by Debunne *et al*. [46]. In this study, the influence of hydrophilic excipients on the *in vitro* drug release from MCC-based pellets was assayed. The use of cyclodextrins (β-CD or hydroxypropyl-β-CD), in a proportion of 20 %, in pellets based on Avicel PH 101 increased the release of piroxicam. As expected, the influence of the less soluble β-CD on the dissolution rate was lower than that of hydroxypropyl-β-CD. However, release from pellets containing hydroxypropyl-β-CD was similar to that from pellets based on a mixture of Avicel PH 101 and CL 611 (MCC co-processed blend containing SCMC). Combining Hydroxypropyl-β-CD (20 %, w/w) with a mixture of Avicel PH 101 and CL 611 (ratio 1:3) had only a minor influence on the dissolution rate. Santos *et al*. [63, 64], used 16 % β-CD in mixtures of MCC/chitosan or MCC/ xanthan gum. Pellets produced by the MCC/xanthan gum/β-CD mixture displayed immediate release of the model drug diclofenac sodium. The release behavior of tablets made of pellets comprising β-CD was anomalous, with diffusional exponent (n) values of 0.625, indicating that drug diffusion and erosion were competing mechanisms of drug release from those tablets.

Bon *et al*. [65] 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 obtained by extrusion-spheronization. These authors compared the
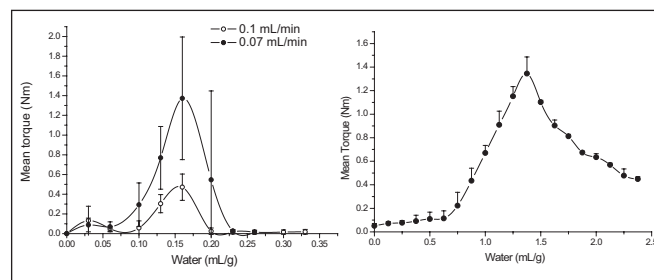

Figure 1 - Effect of addition rate of water on β-CD masse consistence during granulation using multiple addition method torque rheometry (mean ± SD; n = 3). Left: β-CD. Right: Avicel PH 101.
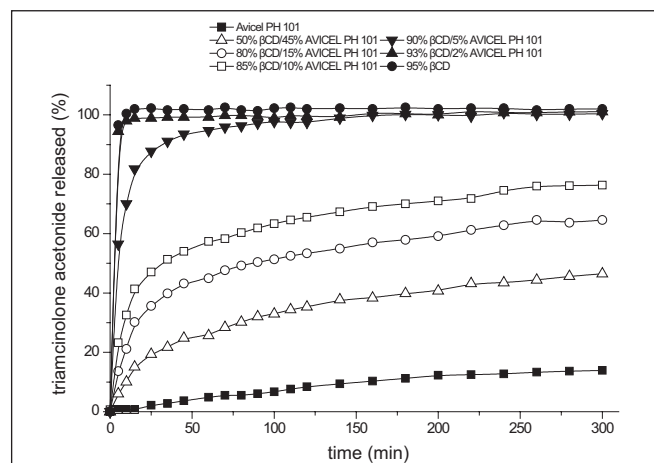

Figure 2 - Release profiles in buffer phosphate pH 6.8 for pellets containing triamcinolone acetonide (5 %) and different mixtures of MCC and β-CD.

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behavior 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 elaborated with cross-linked β-CD-based polymer disintegrated completely, thus accelerating dissolution of nimesulide (75 ± 2 % in 120 min vs. 12 ± 1 % for pellets with only MCC). Pellets containing the same amount of β-CD did not disintegrate and the dissolution was much lower (35 ± 1 % after 120 min). This is another example of how the incorporation of high water soluble substances is not sufficient to produce the disintegration of pellets with MCC, but requires other excipients with high water holding capacity and swelling.

Finally, the use of linear dextrins, white and yellow dextrins, has been also proposed as extrusion-spheronization aids in mixtures with different starches [66, 67]. This topic will be described in a later section (2.1. Starches).

2. Polysaccharides
2.1. Starches

Starch is one of the most important and versatile excipients and has innumerable industrial applications, including in the pharmaceutical industry. Starch is a polysaccharide comprising glucose monomers joined by α-1,4 glycoside linkages. Native starch consists of a mixture of two types of molecules: the linear and helical amylose and the branched amylopectin. Depending on its origin, starch generally contains amylose:amylopectin (Am:Ap) in a ratio of about 1:3-1:4. Amylose forms a colloidal dispersion in hot water, whereas amylopectin is completely insoluble. The structure of amylose consists of long polymer chains of glucose units connected by an alpha acetal linkage. The amylopectin structure is composed of linearly α(1→4) linked glucose units with occasional α(1→6) glycosidic bonds which provide branching points.

Most natural commercial starch is extracted by different techniques from corn, wheat, tapioca, rice and potato. Normally, components are separated by physical means (grinding or crushing) and the resulting pulp is mixed with water and purified. Finally, the starch-containing paste is dehydrated and dried. There are also various chemically modified starch derivatives of high technological value in both food and pharmaceutical applications. Starch derivatives are commonly prepared by oxidation, esterification, hydroxyalkylation, dextrinization and cross-linking of the original starch. Such derivatives have a better response to pH changes and temperature increase, better stability and modified native starch properties such as water absorption, swelling, viscosity and thickening capacity, binding and aggregation behavior and retrogradation. Resistant starch, a highly retrograded starch fraction, is another useful starch derivative often used in food processing with high commercial and nutritional values. These highly retrograded starches are called resistant starch because they are resistant to stomach acid and digestive enzymes but are extensively fermented by the colonic microflora producing butyrate among others (a regulator of colonic cell growth and differentiation) [68-69].

Since O'Connor *et al.* [70] proposed native starches as possible excipients for producing pellets by extrusion-spheronization, several authors have studied these materials either in blends or as binding agents to produce pellets with or without MCC.

Otsuka *et al.* [71] 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 flowability and mechanical strength. The authors concluded that pellets made of starch and lactose were useful as raw materials for coated granules but too hard for use as raw materials for tablet preparation, although they did not provide any data on morphological characterization or drug release.

Starch-based pellets were also obtained by use of mixtures of 67.5 % MCC and 30 % native corn starch by Junnila *et al.* [72, 73]. However, in this case, the high proportion of starch led to defects in

pellet shape and surface texture. Adding polysorbate 80 as a surface-active agent slightly improved wetting and shape, although the effect was not sufficient to produce fully round pellets. This group subsequently proposed the use of waxy corn starch as a co-adjuvant for pellets produced by extrusion-spheronization [72, 73]. It was found feasible to replace up to 40 % of the weight of MCC, thereby considerably reducing the formulation costs. Pellets containing 50 % waxy corn starch were of poorer quality (with the shape at the limit of acceptability) but superior to those containing 30 % corn starch. No drug release data was provided for these pellets.

Different mixtures of starch have been evaluated as excipients for producing MCC-free pellets by extrusion-spheronization, by Almeida Prieto *et al.* [66, 67, 74-76]. The studies performed with mixtures of native starches (corn starch or wheat starch) and with waxy corn starch or dextrin (white or yellow) as binders demonstrated that pellets with acceptable morphometric characteristics can be prepared by extrusion-spheronization. Results showed that starches have a much lower capacity to retain water than MCC, but that inclusion of binders significantly improved this capacity [67]. Rheological properties of wetted masses determined by torque-rheometry [67, 72] showed that the consistency of corn and wheat starches masses is not suitable for extrusion-spheronization. The optimal water content was within a much narrower range for starches than for MCC, with significantly lower maximum torque values than those obtained for MCC. In addition and particularly in the case of wheat starch, the rheometric data indicated that water is not homogeneously distributed within the mass and that the optimal amount of wetting agent was difficult to determine. Only small amounts of water were required to achieve the capillary state. Adding white or yellow dextrin or waxy corn starch as binders provides consistency, resistance and plasticity of wetted mixtures, thereby improving the rheological properties of native starches. Using these mixtures enabled good quality pellets to be produced. Good size and shape distributions of spherical pellets were obtained with both corn starch and wheat starch, with white dextrin as binder (*Figure 3*). Nevertheless, the shape of the pellets obtained with the highest proportions of waxy corn starch was poorer and the results suggested that better shapes might be obtained with waxy corn starch at proportions of less than 10 %. Drug release behavior of pellets containing triamcinolone acetonide as a model low dose, poorly water soluble drug [66, 75, 76] showed that the release rate could be modulated by choosing an appropriate mixture of binder/starch. Wheat- or maize-starch-based pellets produced with 20 % white dextrin quickly disintegrated in contact with the dissolution media releasing the drug almost completely within 20 min, whereas maize-starch-based pellets containing 5-35 % of waxy maize starch swelled in release media and displayed controlled release over periods of 9-12 h or longer when prepared with appropriate amounts of granulation fluid.

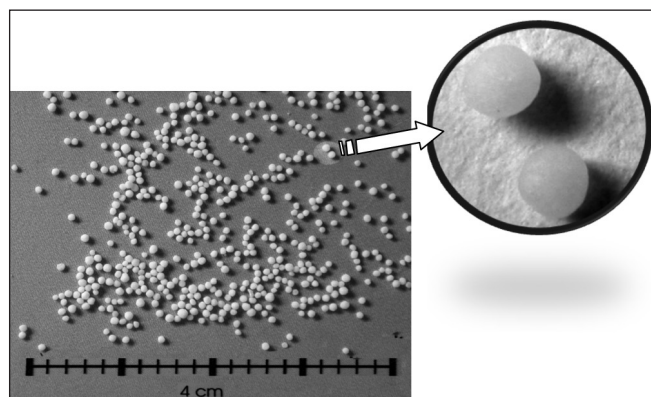Since 2005 our group has also been studying the possibility of

Figure 3 - Macrophotography of spherical pellets obtained with mixtures of wheat starch and white dextrin as binder by extrusion/spheronization.

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using mixtures of modified or resistant starches with different binders, such as gluco- or galactomananes, to fabricate high quality pellets by extrusion-spheronization [77-79]. Modified and resistant starches prevent attack by human digestive enzymes and fermentation in the large intestine. Thus, pellets comprising resistant starches reach the large intestine intact, thereby favoring controlled release of the drug throughout the digestive tract. In these studies, pellets were elaborated with mixtures containing 83 %/10 %/2 % or 73 %/20 %/2 % starches (modified or resistant) /binder (gluco or galactomanane)/drug (tri-amcinolone acetonide) and water as granulating liquid. The starches assayed were a waxy-based acetylated maize starch (Resistamyl 347), a cross-linked corn starch (Mira-cleer 187), a retrograded resistant high-amylose type 2 starch (Novelose 240), a retrograded resistant high-amylose type 3 starch generated from the hydrolyzed products of corn starch (Novelose 330), native amylose corn starch (Hylon VII), a retrograded resistant high-amylose type 2 starch prepared hydrothermally (Hi-maize 1043) and finally amylopectin-rich native starch (potato starch). Most of the mixtures displayed similar behavior to those obtained by Almeida *et al*. [67, 76] with mixtures of native starches (corn starch or wheat starch) and waxy corn starch, which produced pellets of a wide range of shapes (spheroidal and cylindrical particles) depending on the type and amount of starch and water added. The use of dextrins instead of mananes may improve the morphometric properties of pellets. Drug release depended largely on starch type and content. A few representative examples of drug release profiles obtained with certain mixtures of modified or resistant starches and galactomananes are shown in *Figure 4*.

De Clauser *et al*. [79] prepared pellets containing the drug triam-cinolone acetonide, with native amylose corn starch (Hylon VII) or mixtures of the starch with binder (Waxy Wheat -WW- or Bean Gum -BG) and with Surelease, or water dispersions of Surelease and WW or BG as granulating agent. Pellets elaborated with WW either mixed with Hylon VII, or dispersed with Surelease were mostly spherical. It therefore appeared that the wetted masses elaborated with waxy corn starch in the wetting agent provided the best viscoelastic properties as well as positive behavior during the spheronization step. Incorporating BG resulted in more elliptical pellets, which increased the Vr value as the proportion of BG was increased in the formulation. Using Surelease without WW or BG provided elliptical, although irregularly shaped pellets. Release from all formulations was independent of pH, with typical TA controlled release profiles and less than 80 % of drug was released in 12 h (*Figure 5*). The presence of WW or BG and use of pregelling native corn starch as wetting agent rendered pellets with high drug release. The inclusion of these materials probably produced swelling and erosion of pellets, resulting in more rapid release of drug. On the contrary, the presence of Surelease as wetting agent gave rise to the slowest and most controlled release of TA, almost irrespective of the pH. The presence of ethylcellulose in the pellets apparently impeded diffusion of water to the interior of particles and later diffusion and release of the drug.

Dukić-Ott, *et al*. [60] also evaluated a modified starch (high-amylose, crystalline and resistant starch, Uni-Pure Ex starch) as an alternative excipient to microcrystalline cellulose for pellets containing anhydrous theophylline (25 %, w/w) [59], hydrochlorothiazide and piroxicam as model drugs. As is common in starch-based pellets, a binder (HPMC) was necessary to obtain an acceptable wet mass adequate for extrusion. Adding sorbitol also improved the surface properties of the pellets by modifying the consistency of the wet mass. A high pellet yield, acceptable sphericity and low friability were obtained. Complete release of theophylline (100 % in less than 20 min for all formulations), hydrochlorothiazide and piroxicam (> 80 % drug release in 30 min) was reported, favored by rapid disintegration of pellets. The drying process had a significant effect on the surface properties of modified starch pellets and thus on the subsequent coating process. The drug bioavailability in dogs, of orally administered
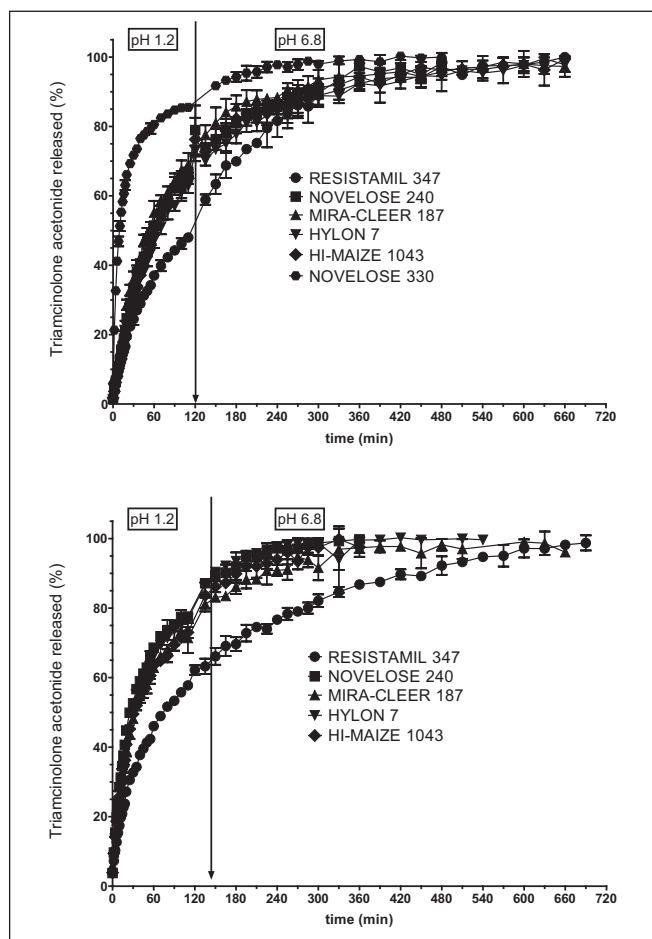

Figure 4 - Release profiles of triamcinolone acetonide for pellets containing 2 % of drug, 78 % (top) or 88 % (bottom) of some commercial resistant starches and locust bean gum (20 or 10 %). The dissolution medium was initially USP simulated gastric fluid (pH 1.2, 37 ± 0.5 °C), but after 2 h was brought to pH 6.8.
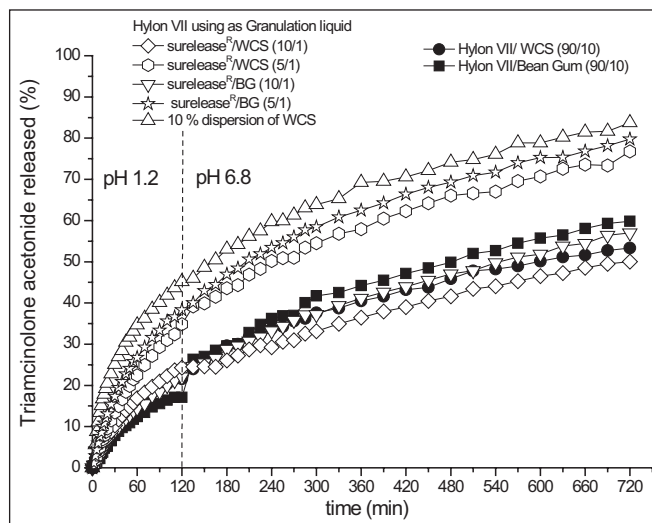

Figure 5 - Release profiles of triamcinolone acetonide for pellets containing the resistant starch Hylon VII in mixtures with Waxy corn starch or bean gum granulated with Surelease (Solid symbols) or granulated with different solutions (open symbols). The dissolution medium was initially USP simulated gastric fluid (pH 1.2, 37 ± 0.5 °C), but after 2 h was brought to pH 6.8.

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hydrochlorothiazide pellets [60] and enteric-coated starch-based piroxicam pellets [80] was similar to fast-disintegrating immediate-release hydrochlorothiazide tablets (Esidrex 50 mg) and immediate release piroxicam capsule (Feldene), respectively.

Certain derivative starches have also been used as disintegrants to increase drug release from MCC-based pellets. Souto *et al.* [14] and Debunne *et al.* [46] investigated the influence of Explotab (sodium starch glycolate and sodium carboxymethyl starch) in pellets elaborated with MCC. Incorporating Explotab into MCC pellets did not lead to their disintegration in drug dissolution medium, although inclusion of this disintegrant did increase drug release.

Some investigators, such as Podczeck [81], consider that the use of starch requires more effort than merely adding water by mixing, which is the usual method used for MCC. This author also pointed out that it is difficult to judge the quality of the pellets in terms of roundness and range of particle size distribution with the data provided in many of the publications on starch-based pellets. This statement is supported by the fact that inspection of photographs provided in these publications reveals that the pellets were "rounded" (elongated with rounded edges) rather than spherical, so that starches do not appear to be a universal replacement for MCC in the pharmaceutical industry. Nevertheless, we believe that MCC-based pellets are rarely fabricated with cellulose as the only excipient (as observed in the previous section and in other studies cited herein). Other materials (fillers, binders, aqueous soluble components, disintegrants, etc.) are often added to improve the properties of MCC pellets. From a technical point of view, extrusion-spheronization of starch/binder mixtures is not necessarily more complicated that pelletization of MCC or MCC/excipient mixtures. Furthermore, detailed morphological analyses of starch-based pellets, including size, shape and surface, have been performed by Almeida *et al.* [67, 76, 79] and Dukić *et al.* [59, 60, 80, 82]. The factors investigated were the morphological parameters: Vr (percentage of variation in radial chord length for a large number of radial chords drawn in the outline of the particle at small angular intervals, with respect to mean radial chord length) and Vp (percentage deviation of measured perimeter from the perimeter of a circle with radius equal to the mean radial chord length of the particle), both proposed in [18-20]) and the aspect ratio (pellets length to pellets breadth ratio) and the shape factor eR (which combines an estimation of length-to-width ratio and perimeter). Using Vr and Vp Almeida *et al.* [76] demonstrated that extrusion-spheronization techniques could be used to produce quality starch-based pellets with similar morphological characteristics to MCC-based pellets. These authors obtained pellets with Vr and Vp values typical of spherical shapes using a blend of 80 % corn starch, 20 % of white dextrins and 5 % of talc (Vr 3.2 and Vp 7.1) or 75 % wheat starch, 20 % of white dextrins and 5 % of talc (Vr 2.4 and Vp 6.6). These values were similar to those obtained for MCC-based pellets (Vr 3.3 and Vp 7.1).

In conclusion, although starch requires additional binding material and the formulations are usually less robust than MCC-based formulations, because of the narrower range of optimal water content [10] starch/binder mixtures may be a good alternative to MCC, especially when fast release of drugs with poor solubility in aqueous media is desired.

2.2. Alginates

Other polymers of natural origin have been used successfully as alternatives to MCC in the extrusion-spheronization process. These novel materials have been used on the basis on their biological compatibility, bio-degradation and non-toxic properties.

Alginate is a linear polysaccharide formed by blocks of linked β-(1-4) D-mannuronate and α-L-guluronate residues. This polyanionic biopolymer has been used in mixtures with MCC, chitosan or MCC/chitosan and with different granulation solutions to produce pellets. For example, Chatchawalsaisin *et al.* [83] proposed the fabrication

of MCC pellets by incorporating two oppositely charged hydrophilic biopolymers, chitosan and sodium alginate. Using paracetamol as the model drug, the authors identified the levels of paracetamol, chitosan and sodium alginate as the main factors involved in the properties of formulations, while the MCC level was less important but still significant. The presence of chitosan and sodium alginate in the formulation affects pellet size and together with the drug levels also significantly affects the *in vitro* drug release. The interaction between oppositely charged polymers over pellet drug release was not observed to have any effect, but pellets containing chitosan disintegrated.

Charoenthai *et al.* [84] suggested the total substitution of MCC in the fabrication of pellets by mixtures of chitosan/alginates. These authors investigated two chitosans of different molecular weight, using water as granulation liquid. Lower molecular weight chitosan (MW, 190 kDa) displayed better pellet forming properties than higher molecular weight chitosan (MW, 419 kDa). Spherical pellets with a maximum fraction of 60 % w/w chitosan could be produced by including 1.25-2.5 % w/w sodium alginate in the formulations. The resulting pellets had acceptable physical characteristics and displayed rapid drug release. Structural determination by means of FT-IR, DSC and ^{13}C CP-MAS NMR indicated the formation of a polyelectrolyte complex between sodium alginate and chitosan, which, according to the authors, may explain the successful pelletization by extrusion/spheronization.

Sriamornsak *et al.* investigated the effect of granulating liquid [85] and type of sodium alginate and/or calcium salts [84] in the preparation of pellets from mixtures of MCC, sodium alginate and 20 % drug. Pellets were characterized by morphological examination and study of theophylline release. Long, dumbbell-shaped pellets were obtained with viscous granulating liquids (PVP, HPMC, SCMC, Acacia gum, pectin acid, citric acid). However, short, almost spherical pellets were obtained by including calcium chloride in the granulation liquid, as this reduced the swelling ability of alginate. The characteristics of the pellets depended on the type of sodium alginate and calcium salt used and in particular the size and shape of the pellets were affected by the amounts of these substances used. Formulations released about 75-85 % of their drug content within 60 min and the release depended on the amount of calcium chloride. Formulations containing higher amounts of calcium chloride in granulating liquid displayed higher release rates for theophylline resulting from the binding of calcium ions to the negatively charged alginate. Different release behavior was observed depending on the solubility of the calcium salts used.

Cross-linking of alginates to calcium ions was also proposed by Kulkarni and Amin [87] in order to mask the unpleasant gustatory sensation of Paracetamol pellets. Alginate pellets were prepared by extrusion-spheronization with mixtures of drug (25 %), sodium alginate (Manugel LBA, 25 %), Avicel PH101 (31 %) and Avicel RC 591 (15 %) and with dispersion polysorbate 80 as granulation liquid. Cross-linking was achieved by immersion of pellets in 5 % calcium chloride solution. Paracetamol release was relatively slow (about 95 % in 45 min), which was attributed to the incorporation of Avicel RC 591. Although the morphological characterization was not exhaustive (sphericity was evaluated by a scoring method with only 20 pellets), the authors concluded that cross-linked pellets were sufficiently spherical and friable to be coated uniformly with flavorings and sweeteners to improve taste, palatability and mouthfeel.

2.3. Chitosan

Chitosan was first used for the functional application in pellets produced by extrusion-spheronization at the beginning of the 1990s, by Goskonda and Upadrashta [88] and Tapia *et al.* [89]. Chitosan is a polysaccharide obtained by N-deacetylation of chitin and is soluble in acidic aqueous solutions. It is a polycationic biopolymer formed by randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine.

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Goskonda and Upadrashta [88] prepared pellets using a combination 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). More viscous grades of chitosan yielded pellets with rough surfaces and slower paracetamol release rate. Pellets prepared with different proportions of chitosan Seacure 342 (0-40 %) and Avicel RC-591 and 20 % of paracetamol or theophylline produced medium-dependent release. Pellets swollen in 0.1 N HCl maintained an intact structure and drug release was slowed down by including greater amounts of chitosan Seacure 342. In water, pellets formed gel-like structures and the release rate increased with chitosan content. Tapia *et al.* [89] showed that it was possible to produce homogeneous pellets by adding a solution of chitosan dissolved in dilute acetic acid (as granulation liquid) to the powder mixture containing MCC. The resulting chitosan fraction in the pellets was as low as 2-3 % w/w. Diclofenac sodium release was considerably slower in formulations containing chitosan (i.e. approx. 100 % in 6 h, rather than in 30 min) demonstrating that effective drug release control can be achieved without the need for the pellets to be coated in polymer.

Santos *et al.* [63] prepared pellets comprising chitosan (4 or 16 %), MCC (50 %), povidone, a filler excipient (lactose, tribasic calcium phosphate and β-CD) and diclofenac sodium as the model drug. Chitosan load and type of filler did not have a major effect on shape and the only factor leading to differences in shape was the type of binding liquid. Nevertheless, an increase in the proportion of chitosan resulted in a significant increase in the surface roughness and in less porous pellets. Pellets containing chitosan with acceptable physical characteristics were obtained when an alcohol/water mixture 50 % (v/v) was used, but in this case effective control of drug release was not achieved.

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 appropriate concentration of acetic acid made the wet mass extrudable, by increasing flexibility and cohesiveness. Powder mixtures containing high proportions of chitosan required higher concentrations of granulation liquid and acid to produce pellets with good morphological and mechanical properties. Increasing the acetic acid concentration up to 0.2 N resulted in a sticky extrudate or pellets with a rod-like appearance. However, no model drug was used in this study and therefore drug release rates were not evaluated.

An attempt was made by Agrawal *et al.* [90, 91] to investigate the use of chitosan in the manufacture of pellets without MMC but including other excipients such as fine particle ethylcellulose (FP-EC) and HPMC, with caffeine as the model drug. Pellets with good mechanical properties were obtained with mixtures containing 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) significantly affected the physical properties of pellets, but not drug release: caffeine was immediately released from the pellets. Increasing the amount of chitosan in mixture produced smaller pellets of different shape and yield.

The degree of deacetylation of chitosan may also exert effects on pellet properties. Jess and Steckel [92] studied the effect of the degree of deacetylation of different grades of chitosan on the extrusion-spheronization process, with budesonide as the model drug and 0.2 N acetic acid solution as granulating liquid. Variable rheological measurements indicated that the degree of deacetylation affected the viscoelastic properties of the wet mass and increased the extrudability. The pellet properties (pellet size and shape, crushing strength and friability) improved with increasing deacetylation levels. Results indicated that only chitosan with a degree of deacetylation > 99 % was suitable for extrusion/spheronization. The degree of deacetylation did not appear

to have a great effect on drug release in these pellets and in all cases pseudo-zero order release kinetics were observed.

2.4 Pectinic acid

Pectin is a structural heteropolysaccharide formed by a complex set of polysaccharides with a basic structure consistent of a linear chain of α-(1-4)-linked D-galacturonic acid that forms the pectin-backbone, a homogalacturonan. Some of the carboxyl residues are substituted as methyl ester or as carboxamine groups and in some regions galacturonic acid is replaced by (1-2)-linked L-rhamnose. The degree of esterification or amidation (% of esterified or amined carboxyl groups) is fundamental in classifying pectins and considerably affects their properties.

The first use of pectin acids in pelletization by extrusion/spheronization was to obtain coated pellets with a gelling film of calcium pectinate. Sriamornsak *et al.* [93, 94] prepared pellets containing theophylline with mixtures of MCC and calcium acetate and HPMC solutions as granulating agents. An insoluble coating of calcium pectinate was obtained by interfacial complexation, by soaking the pellets in an aqueous solution of pectin. Nevertheless, Tho *et al.* [95-100] were the first researchers to investigate the possible use of pectin acids as extrusion-spheronization aids. These researchers investigated the capacity of obtaining spherical pellets using different types of pectin (degree of methoxylation (DM) 35-72 and amid substitution). Not all pectins are capable of producing spherical pellets [97, 98] because swelling of pectins with a low degree of methoxylation causes a lack of appropriate rheological properties of wetted mass. However, incorporating ethanol, citric acid or calcium chloride have been shown to improve the pelletization process for certain types of pectin assayed [96]. In order to identify the best granulation liquid for producing pellets from mixtures containing highly methoxylated pectin, Tho *et al.* [97] used quantitative structure-activity relationships (QSAR) and quantum chemical descriptors. These authors concluded that irrespective of the grade of pectin used, the two most important factors for substances added to water in the granulation liquid were molecular size and the ability to form hydrogen bonds. Including small polar molecules in the granulation liquid resulted in the production of pellets of better size and shape from pectin mixtures. Finally, reducing the solubility of pectins, by changing the polarity of the granulation liquid, resulted in major improvements in the extrusion/spheronization process.

A very low soluble pectin-derivative (pectinic acid, degree of methoxylation 4 %) was found to be a good excipient for pelletization by extrusion/spheronization [98]. Based on the results of the latter study, pellets containing 10 % pectinic acid with 4 % methoxylation, were prepared and compared with MCC-based pellets [99]. Results showed that drug release from pellets based on pectinic acid or MCC was independent of pH when riboflavin or paracetamol were used as model drugs, but that faster drug release was achieved in acidic media with theophylline as the model drug. The authors concluded that, as with starches, the pelletization properties of pectinic acid were not as universal as MCC, but showed advantages as regards formation of disintegrating pellets, which provide fast release of low soluble drugs. Tho *et al.* [100] proposed reducing the solubility of pectins as a method of controlling swelling and consequently, of optimizing the extrudability of the mass containing this heteropolysccharide. They therefore studied the cross-linkage of amidated low-methoxylated pectins with different degrees of amidation by means of formation of an insoluble complex with calcium. Amidated pectin was used because it is more reactive to calcium ions than pectin. The degree of amidation and the concentration of calcium ions added, as well as the interaction between the two, were identified as significant factors in the preparation of spherical pellets.

2.5. Carrageenans

Carrageenans or carrageenins are also polysaccharides that have

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been evaluated as excipients in extrusion/spheronization. These polysaccharides are a family of linear sulfated polysaccharides of high molecular weight formed by sulfated and non sulfated units of galactose and 3,6 anhydrogalactose linked by α(1-3) and β(1-4) glycosidic bonds. There are three main commercial classes of carrageenan (*Figure 1*): kappa, iota and lambda, which differ fundamentally in their solubility, swellability and behavior in the presence of ions. Lambda-carrageenan does not gel, kappa-carrageenan interacts with calcium and potassium ions forming brittle and strong and rigid gels, respectively, and iota-carrageenan is able to form elastic and soft gels with calcium ions.

Carrageenans were used in the extrusion-spheronization process by Garcia and Ghaly [101] to produce bioadhesive pellets. Kappa-carrageenan was included (10 to 30 %) in pellets containing MCC and co-processed MCC containing 11 % SCMC, with water as the granulating agent. Pellets of between 1.16 and 1.69 mm and of low friability were obtained but no morphological analysis was carried out. *In vitro* bioadhesion and glipizide release from bioadhesive pellets was affected by the level of carrageenan and the presence of SCMC. As the percentage of carrageenan increased, drug release decreased and bioadhesion increased. Pellets made from co-processed MCC containing SCMC also displayed slow glipizide release and better *in vitro* bioadhesion than MCC pellets. Bioadhesion was increased with carrageenan and SCMC content.

Bornhöft *et al*. [102] studied three varieties of carrageenan, iota-, kappa- and lambda-carrageenan, with the aim of obtaining a suitable alternative to MCC and used α-lactose monohydrate as filler. Iota- and lambda-carrageenans resulted in extrudates that could not be spheronized and kappa-carrageenan produced extrudates with suitable plastic and brittle properties for the spheronization process. A minimum of 5 % of kappa-carageenan was necessary to produce pellets without MCC. The properties of the resulting pellet using both materials were comparable but the optimal water content differed. Kappa-carrageenan requires more water than MCC to produce spherical pellets. An increase in the range of optimal water content improved the robustness of the pelletizing process, but binding more water could lead to stability problems with sensitive drugs.

Thommes and Kleinebudde [103, 104] prepared pellets containing 20 % of kappa-carrageenan with different fillers (lactose, mannitol, maize starch and dicalciumphosphate dehydrate) and drugs (acetaminophen, theophylline, mesalamine and hydrochlorothiazide). Results showed that most pellets were of acceptable quality regarding size, size distribution and shape. The effects of different fillers on the pelletization process and the pellet properties were negligible. In contrast to MCC pellets, drug release from kappa-carrageenan pellets was much less affected by the solubility of the drug. Pellets containing kappa-carrageenan disintegrated in less than 10 min. Irrespective of the filler used, the release was completed within less than 20 min. Release of hydrochlorothiazide and theophylline from pellets containing carrageenan was not influenced by the dissolution media (water or 0.1N HCl). Nevertheless, the drying process was crucial and had a significant effect on the properties of the pellets containing kappa-carrageenan [105].

Recently, Thommes *et al*. [106] performed a single-dose pharmacokinetic study of pellets containing the poorly soluble HIV-protease inhibitor darunavir in dogs and demonstrated that the bioavailability of the drug was higher in kappa-carrageenan beads than in MCC pellets because of rapid disintegration of the former. The authors calculated the drug bioavailability relative to that of a marketed tablet (Prezista) and obtained a relative bioavailability of 155 % for the kappa-carrageenan bead formulation and of 2 % for the MCC-based pellet.

Pellets based on kappa-carrageenan were compared with MCC-based pellets containing disintegrant (SCMC) or pore former (PEG 6000) [107]. For this purpose, pellets containing 77-90 % of vatalanib succinate (SAG/ZK) or theophylline were prepared. All batches showed acceptable yields and morphological and mechanical properties. Inclusion of MCC or kappa-carrageenan enabled production of pellets containing up to 90 % of drug. The MCC pellets did not disintegrate and drug release was predominantly controlled by diffusion and limited by low drug solubility. Inclusion in MCC pellets of SCMC or PEG 6000 significantly modified the dissolution by altering the apparent drug diffusivity in the matrix (drug diffusion coefficients varied between 0.36 and 29 × 10^{-6} cm^2/s). In contrast, pellets containing kappa-carrageenan were much more porous and disintegrated rapidly, resulting in rapid release of drug within a few minutes, even in the case of high doses of drugs of low/poor aqueous solubility.

Finally, Santos *et al*. [64, 108] prepared pellets without MCC, with the polysaccharide xanthan gum with the aim of investigating pelleting behavior. Pellets were prepared by extrusion-spheronization of mixtures of sodium diclofenac or ibuprofen (10 % w/w), xanthan gum (16 % w/w) and one of three different fillers (monohydrated lactose, tribasic calcium phosphate or β-CD) at 16 % w/w. Tablets were produced with a single punch press (max. punch pressure of 125 MPa) and flat-faced punches (1.00 cm diameter). The result of compression was permanent deformation and compaction of pellets. Furthermore, the pellets lost part of their sphericity and porosity as a result of compression. The integrity of the pellet was destroyed in the first hour of dissolution test due to disruption of the agglomerate structure as a result of the excessive swelling of the gum at a concentration of 16 %. Tablets prepared by compressing pellets did not function as multiparticulate systems. Ibuprofen was released in a bimodal mode with a Case II transport mechanism, whereas release of diclofenac sodium was anomalous and characterized by drug diffusion and erosion mechanisms.

3. Synthetic polymers
3.1. Polyacrylates

Vila Jato *et al*. [109] proposed the use of some varieties of polyacrylic acids (carbopol or carbomer) with the aim of producing bioadhesive pellets containing carvedilol as drug, by means of extrusion-spheronization. Two types of carbopol (974P and 971P) (cross-linked polyacrylic acids) were assayed. Mixtures of MCC containing 10 or 20 % of these types of carbopol were prepared with isopropyl alcohol as the granulating agent, in order to prevent swelling of polyacrylic acids. The pellets displayed good mechanical and morphological properties and effective control of carvedilol release was obtained in media simulating intestinal conditions, probably as a result of the swelling capacity of carbopol in neutral or basic pH. However, no control of drug release was achieved in acidic media. Rodriguez Gomez *et al*. [110] evaluated the effect of substituting isopropyl alcohol with isopropyl alcohol/water mixture as granulating agent in the production of pellets containing these varieties of carbopol and with 10-30 % diclofenac sodium as model drug. Using a rotational central composite design with four factors (carbopol level, drug charge, volume of granulating agent and water content) and eighteen treatments, the authors demonstrated that water was the main factor affecting the size and morphology of pellets, irrespective of the type of carbopol used. The drug also favored extrusion-spheronization of wetted masses and more spherical pellets with a narrow size distribution were obtained when high concentrations of drug were used. Differences in drug control release depended on the type of carbopol used. Release of diclofenac sodium was controlled in simulated intestinal fluid, pH 7.4 when carbopol 971P was used, but the entire dose was released in 30-60 min in carbopol 974P-based pellets. The authors attributed the differences in release to the different gel structure [111] obtained with these two varieties of polyacrylic acid.

Neau *et al*. [112] also proposed the use of carbopol 974P NF resin to prepare pellets by extrusion-spheronization. In this case, the authors proposed the use of strong electrolytes (such as sodium chloride, calcium chloride, magnesium chloride and aluminum chloride) as granulating agents to prevent handling difficulties in the granulation and extrusion

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step due to the slightly adhesive nature of carbopol when it is wetted with water. The presence of cations in water was found to reduce the adhesiveness of wetted carbopol. Pellets containing mixtures of MCC and 10-55 % of carbopol were prepared with or without 5 % of chlorpheniramine maleate as the model drug. The adhesive force of wetted mixtures of MCC and carbopol 974P decreased dramatically in the presence of strong electrolytes and was greater when high charge density electrolytes were used. Studies carried out to optimize the carbopol pellets [113] showed that increasing the carbopol content resulted in a significant reduction in the percentage of drug released. High quality beads with the long duration of drug release were produced by combining high carbopol content, high water content, low calcium chloride levels with low speed spheronization for long times. Drug release from carbopol 974P-based pellets was also influenced by the nature of the drug [114]. Nonelectrolyte drugs (caffeine and dyphylline) were released faster than salts of weakly basic drugs (chlorpheniramine maleate and diphenhydramine hydrochloride), suggesting ionic interactions between the protonated amines of the salts and the carboxylates of the carbopol resin.

Gómez-Carracedo *et al*. [45, 115-118] evaluated the effects of several process variables on properties of pellets obtained from blends of MCC and carbopol 934 or MCC carbopol 974P using calcium chloride as granulating agent. Many factors were investigated: the influence of process variables (carbopol:MCC ratio, wetting liquid proportion, CaCl2:carbopol ratio) [115], drying conditions (oven-drying and freeze-drying after slow or fast freezing) [118] and the influence of incorporation of intragranular excipients (lactose or dicalcium phosphate) [45, 117]. When carbopol 934 was used, the consistency of masses was mainly influenced by the proportion of $CaCl_2$, while mean pellet diameter was affected by the carbopol:MCC ratio and/or presence of theophylline. Differences in theophylline release kinetics were attributed to differences in pellet size and theophylline hydration state [115]. It was possible to modulate the microstructural, morphological and mechanical properties of MCC carbopol 974P by controlling the drying step and the proportion of $CaCl_2$. The drying step determined the porosity parameters that appeared to be critical factors for achieving controlled release of theophylline and ketoprofen [118]. The drying procedure was also critical in theophylline pellets containing MCC, carbopol and certain intragranular excipients such as lactose [45] or dicalcium phosphate [45, 117]. The drying procedure also had an important effect on pellet size and porosity. Theophylline release from pellets was completed in less than 30 min and followed first-order kinetics, with a rate closely related to the intragranular porosity.

Mezreb *et al*. [119] discussed the possibility of producing bioadhesive pellets containing mixtures of MCC and carbopol 974P (10 to 20 %) or 971P (10 %), with water as wetting liquid. These authors demonstrated that the use of electrolytes such as $CaCl_2$ to eliminate the problem of the adhesiveness of polyacrylic acids is possible because of the decrease in their bioadhesive properties brought about by disturbing the interactions between carboxylate groups. They therefore studied the possibility of producing bioadhesive pellets containing either CP 971P or CP 974P, with water as wetting agent, in order to maintain the bioadhesive nature of the pellets, by modifying the process variables extrusion speed, spheronizer speed and spheronization time and the formulation variable, amount of water. Low extrusion and high spheronizer speeds were required to produce spherical pellets and better yield. The authors reported optimal speeds of 30 rpm in extrusion and 960 or 1300 rpm in spheronization for producing pellets containing 10 % carbopol 971P (with 45 % water) or 20 % carbopol1 974P (with up to 58 % of water), respectively.

The use of poly(N-isopropyl acrylamide) to produce a sustained release matrix or photopolymerization of coated MCC pellets has been proposed by Mayo-Pedrosa *et al*. [39, 120]. Theophylline pellets and granules were prepared with powdered cellulose, poly(vinylpyrrolidone) and 15 % poly(N-isopropyl acrylamide). Spherical powdered cellulose-based pellets were obtained by adding up to 24 % of poly(N-isopropyl acrylamide) or combining both poly(vinylpyrrolidone) (20 %) and poly(N-isopropyl acrylamide) (15 %), as a result of the low consistency and high plasticity of the wet masses. Pellets and granules containing both PVP and PNIPA displayed enhanced, although limited, ability to control theophylline release. Release rate was notably reduced by compression of the pellets or by coating pellets with a polymer film by photo-polymerization/ cross-linking of poly(N-isopropyl acrylamide) monomers on the pellet surface, using a photoinitiator and UV-irradiation at 366 nm. Coating did not significantly change the shape, size or friability of the pellets, but considerably decreased the porosity and sustained drug release for several hours.

Methacrylic acid and methacrylate polymers (Eudragit) are acrylic resins frequently used for coating pellets and granules. Some researchers have proposed the use of these polymers as granulating agents or in mixtures with extrusion-spheronization aids to achieve controlled release of drugs from pellets.

One of these approaches was carried out by Bianchini *et al*.[121]. In this study, aqueous dispersions of ethylcellulose (Aquacoat) or acrylic resin (Eudragit RL/RS 30D) with fumaric acid were used as granulating agent to obtain MCC/lactose-based pellets with effective drug release in a single step, without any coating process. Including these water-insoluble polymers did not appear to affect the extrusion-spheronization process. On the basis of visual observations, the authors concluded that it was possible to obtain spherical granules with smooth surfaces. Incorporating Eudragit RL/RS 30D produced a homogeneous matrix that provided prolonged drug release. Similarly, Wang *et al*. [122, 123] studied how the use of aqueous dispersions of acrylic resins (Eudragit L 30 D, NE 30 D and RS 30 D) as a granulating binder affected the mechanical properties of MCC/lactose pellets. The type of polymer and incorporation of plasticizer affected the susceptibility of the moistened extruded granules to the shearing forces applied during the spheronization process, which influenced the surface morphological properties of the pellets. Morphological, microstructure, flow and packing properties were also studied by Rodriguez *et al*. [124], with Eudragits L30D-55 as the granulating agent.

Krogars *et al*. [125] used a three-factor central composite design to study the influence of the amount of Eudragit S 100 and citric acid in pellets containing 30 % of ibuprofen and 48-49 % of MCC. Eudragit S 100 in ethanol (60 %) solution was used as a binding solution. Inclusion of Eudragit S100 increased the size of the pellets and modified the sphericity. Pellet roundness increased when small amounts of acrylic resin were used but decreased when large proportions of resins were used. Nevertheless, no delay in drug release was obtained with matrix pellets containing Eudragits S100.

Mehta *et al*. [126]. prepared pellets without MCC, based on a mixture of Eudragit L 100 55 and Eudragit S 100, with triethyl citrate as a plasticizer, thiazole-based leukotriene D antagonist as the model drug, polyvinylpyrrolidone as the binder and water as the granulating agent. The effects of drug loading, the amount of water required for granulation, spheronization time and triethyl citrate content were studied in relation to drug release rate, although size and shape were not evaluated. Drug loading, amount of granulation water and spheronization time were found to have important effects on the porosity of the pellets (pore size distribution, total pore surface area and shape and morphology of pores) and subsequently on drug release. Adding triethyl citrate to the pellet core also modified the drug release properties. Release studies demonstrated that drug release occurred due to matrix erosion via a surface erosion mechanism, an increase in porosity increased the area of contact between the release medium and the surface of the pellet, resulting in faster hydration and consequently higher erosion rates. Abbaspour *et al*. [125] studied Eudragit RS PO and Eudragit RL PO and a combination of these to produce control-

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led release pellets containing ibuprofen. Most of the pellets were of adequate size, shape and hardness however no significant delay in drug release was obtained.

3.2. Poly(vinylpyrrolidone)

Poly(vinylpyrrolidone) (PVP) is a polymer frequently used as a binder in powder mixtures with other components such as MCC [39, 63, 126-133], or dissolved in the granulating liquid [134]. PVP reduces the water requirements in the granulating step, improving the extrusion-spheronization process and producing more uniform and spherical pellets with a narrower particle size range when compared with the same formulations obtained without PVP. Furthermore, PVP usually has a strong effect on drug release, depending on the composition of pellets, but a generally slower release rate was observed after incorporating increasing amounts of this binder.

A PVP derivative has also been proposed as an alternative to MCC in the extrusion-spheronizacion process. Liew *et al*. [135] evaluated three grades of cross-linked poly(vinylpyrrolidone), a synthetic water-insoluble cross-linked homopolymer of N-vinyl-2-pyrrolidone, mainly differing in particle size, as possible pelletization aids in binary mixtures with lactose. The two finer grades of cross-linked poly(vinylpyrrolidone) were found to produce good quality pellets, comparable to MCC pellets and the authors indicated that the mechanism of pellet formation resembled the sponge model proposed for MCC. Polymer concentration and water level were found to be the most critical parameters in the pelletization process. Nevertheless, inclusion of a drug was not found to have any effect and thus, release behavior was not studied. Verheyen *et al*. [136] recently confirmed the ability of finer grades of cross-linked poly(vinylpyrrolidone) as pelletization aids and elaborated crospovidone-based pellets containing different amounts of Paracetamol, hydrochlorothiazide and spironolactone as model drugs. The results showed that it is possible to produce pellets with up to 60 % (w/w) active pharmaceutical ingredients (API) and in which quality is maintained by using fine grade qualities of crospovidone aspects. Pellets containing binary mixtures of the poorly-soluble APIs and crospovidone disintegrated (unlike MCC-based pellets), resulting in fast drug release. Crospovidone may therefore be a good alternative to MCC in starch-binder mixtures, especially when fast release of drugs with poor solubility in aqueous media is desired.

Finally, other materials have been proposed for improving the properties of MCC-based pellets or as alternatives to MCC in extrusion-spheronization, such as glyceryl monostearate [55, 133, 137-139], mixtures of glyceryl monostearate/barium sulphate [81, 140, 141], polyethylene glycol (PEG) [55, 142-145] and methoxypolyethylene glycol (MPEG) [146], polyethylene oxide (PEO) [146], Gelucire [147, 148], non-ionic surfactants (i.e., polysorbate 60 and 80, sorbitan monostearate and sorbitan monooleate) [50, 72, 142, 149-152], oils (mono and diglycerides systems) [151-154] and Solutol HS15 [154].

<div align="center">*</div>

A wide variety of materials have been tested for the total or partial replacement of MCC with the aim of meeting various technological and therapeutic demands, mainly modifying mechanical properties or modulating drug release profiles from pellets. Despite the considerable research efforts made, the materials tested up to now lead to formulations that are usually less robust than MCC-based formulations and require additional auxiliary excipients in order to improve the features of the pellets. Nevertheless, the state-of-the-art on non-MCC pellets identifies a single material suitable for overcoming specific handicaps of MCC-formulations (such as disintegration ability) or providing them with novel features, namely site-specific delivery or sustained release. In most cases it was necessary to combine excipients in order to obtain mixtures adapted to the extrusion-spheronization process. Overall, published results showed that a mixture of a filler with a binder,

especially those that promoted the water-hold capacity and restrict water migration, resulted in a paste with good extrudability that could produce spherical pellets. Binders with ability to incorporate water and swell, forming high viscous gel, should be used in low proportions in order to obtain low elastic wet mix with good deformation properties to produce spherical pellets whereas binders that incorporate water without increasing the elasticity of the masses (i.e. dextrins) should be incorporated in higher proportions to maintain the sphericity of pellets. In conclusion, although a single excipient would be the ideal alternative to MCC, mixtures of good candidates as fillers and binders (based on their release properties) might be a good choice for preparing non-MCC pellets for extrusion-spheronization.

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