Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 371–380
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Disintegrating pellets from a water-insoluble pectin derivative produced by extrusion/spheronisation

Ingunn Tho[a,*], Sverre Arne Sande[a], Peter Kleinebudde[b]

[a]*Department of Pharmaceutics, School of Pharmacy, University of Oslo, Oslo, Norway*
[b]*Institute of Pharmaceutical Technology, Heinrich-Heine-University, Düsseldorf, Germany*

Received 13 February 2003; accepted in revised form 30 April 2003

Abstract

Pectinic acid (PA) and microcrystalline cellulose (MCC) as extrusion aiding excipients have been compared. Three different drugs were selected as models: Riboflavin with a very low water solubility, paracetamol and theophylline as drugs with high water-solubility. The drug load was varied from 1 to 80% wt. The low-soluble pectin derivative, PA (degree of methoxylation $<10\%$) was found to be well suited as an extrusion aiding excipient in pellet preparation by extrusion/spheronisation. The substance has a high drug loading capacity and produces disintegrating pellets that are well suited for fast delivery of drugs with a low water-solubility. The pellets are also mechanically stable. Compared to MCC, PA was found to require less water for pellet formation and was more sensitive against changes in the water content. In order to achieve optimal shape of the pellets, spheronisation was carried out at 45 °C. PA is more sensitive to type and amount of drug and is, consequently, not as universally applicable as the conventionally used microcrystalline cellulose. The great advantage of pectinic acid is, however, the disintegrating properties of the pellets after only a short time of exposure to liquid.

Keywords: Pectinic acid; MCC; Pellets; Extrusion/spheronisation; Mechanical stability; Disintegration

1. Introduction

Most drugs do not possess the properties required for successful pelletisation by extrusion/spheronisation. Addition of an aiding excipient is therefore required to produce formulations with the necessary rigidity, plasticity and water absorbing capacity to allow production of spheres. Microcrystalline cellulose (MCC) has come to be regarded as an essential component for successful extrusion/spheronisation, possible by favourably altering the rheological properties of the wet mass [1–3]. A disadvantage of MCC is that pellets based on this excipient usually do not disintegrate, which result in slow drug release, especially for low soluble drug substances [4,5]. The amount of MCC as well as the water level will naturally influence the drug release rate of the resulting pellets [3,4,6]. One approach to achieve disintegrating pellets from MCC has for instance been the use of powdered cellulose as a substitute for MCC [7], but a binder had to be added in order to obtain pellets. Another was granulating MCC with ethanol/water mixtures [8], which resulted in mechanically weak pellets. The use of MCC might also be undesirable due to stability issues of the drug substance [9]. Consequently, other excipients have been studied as an alternative to MCC during the last years; exemplified by kaolin, weak acids or bases and waxy materials [10], waxy corn starch [11], formulations containing two or more of the components barium sulfate, glycerol monostearate and lactose [9], lactose alone [12], and pectin [13].

Recently, a low soluble pectin derivative (pectinic acid, DM 4%) has been shown to possess great capacity as an extrusion aiding excipient suitable for pelletisation by extrusion/spheronisation [14]. Pectin is a naturally occurring polysaccharide with a backbone of polygalacturonic acid, and pectinic acid (PA) is defined as a pectin derivative with a degree of methoxylation below 10%. A model system based on different combinations of PA and lactose showed promising results with respect to preparation of MCC-free, disintegrating system that could be suitable for fast delivery of low soluble drug substances [14].

* Corresponding author. Department of Pharmaceutics, School of Pharmacy, University of Oslo, P.O. Box 1068, Blinden, N-0316, Oslo, Norway. Tel.: +47-22-85-79-05; fax: +47-22-85-44-02.
E-mail address: ingunn.tho@farmasi.uio.no (I. Tho).

0939-6411/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0939-6411(03)00071-7

The aim of this study was to optimise the preparation of PA pellets and compare the products to MCC pellets of corresponding formulations. The characteristics of main interest were shape and size of the pellets, hardness and drug release profiles as well as drug release mechanism.

2. Materials and methods

2.1. Materials

Pectinic acid with a DM of 4% (Classic AU-L 049/01, Lot no. 0 106 214, Herbstreith and Fox GmbH, Germany) and microcrystalline cellulose (MCC Sanaq 102 G, Lot no 210207, Pharmatrans Sanaq, Switzerland) were evaluated at different concentration levels as extrusion aiding excipients for three different drugs (paracetamol, theophylline and riboflavin; all from Sigma-Aldrich Chemie GmbH, Germany). Fumed Silica (Aerosil 200, Degussa, Germany) was added to improve the flow properties of the powder mixtures with high amount of paracetamol (80% w/w). De-ionised water was used as granulation liquid.

2.2. Characterisation of pectinic acid

Solubility of the pectinic acid (PA) was estimated based on densitometric measurements. A saturated solution of the polymer in water was prepared and left at room temperature 24 h for maximum dissolution. The sample was subjected to centrifugation at 3800 rpm for 1 h. The supernatant was collected and the density determined using a density meter (DMA 5000, Anton Paar, Austria). The maximum solubility was extrapolated from calibration curves of concentration versus density.

The carbohydrate composition was determined quantitatively by methanolysis and gas chromatographic analysis as described by Samuelsen and co-workers [15]. Samples of 1 mg were subjected to methanolysis with 6 M HCl in anhydrous methanol for 24 h at 80 °C followed by trimethylsilylation. Identification and quantification of the monosaccharides were performed on the basis of standards and by using mannitol as an internal standard.

Content of elements (Ca, Na, K, Fe, Mg, Ba and Sr) was analysed with a Varian VISTA Axial CCD simultaneous inductively coupled plasma-atomic emission spectrometer (ICP-AES; Australia). The instrumental conditions were: plasma power 0.95 kW; argon plasma flow 15 l/min; argon auxiliary flow 1.5 l/min; argon nebuliser flow 0.9 l/min and pump rate 15 rpm. As the raw material was insoluble in water the sample was fully hydrolysed with 0.1 M NaOH (5 ml to 500 ml solution) prior to testing. Quantification of each element was performed based on standards. All results were corrected for the content of elements in the solvent (blank).

2.3. Physical characteristics of the extrusion aiding excipients

The water content of the raw materials was determined as loss on drying to constant weight in a vacuum oven at 40 °C and 10–20 mmHg.

Average particle size and particle size distribution of the raw materials were examined by a laser diffraction analyser (Rodos, Sympatec Helos, Germany) at a focal length of 200 mm, corresponding to a measuring range of 1.8–350 μm. The air pressure was set to 1 bar and the measuring time was 5 s. Each sample was measured in triplicate. The particle size distribution was averaged, and the raw materials were characterised as 50 or 90% below the given particle size (D50 and D90).

2.4. Preparation of pellets

Pellets were prepared from the raw materials as obtained from the producer. The extrusion was performed using a twin-screw extruder (Micro 27 GL-28D, Leistritz, Germany) equipped with an axial screen with 23 dies of 1 mm diameter and 2.5 mm length. The extrusion took place at constant screw speed of 100 rpm. Immediately after extrusion the extrudate was rounded in a spheroniser (RM 300, Schlüter, Germany) with a cross-hatched plate of 300 mm diameter at 1000 rpm for 5 min. The spheronisation step was carried out at room temperature for the MCC pellets and at 45 °C for the PA pellets. The pellets were dried in a fluid-bed dryer at 50 °C for 30 min (ST 2 EX, Aeromatic, Switzerland).

For each formulation different combinations of powder feed rate and pump rate were tested in order to find a suitable moisture level for production of spherical pellets. The extrudate water content was varied in steps of approximately 2%.

The water content of the extrudate was determined as the loss on drying after 24 h at 105 °C; tested in triplicate.

2.5. Size and shape of the pellets

The pellets were characterised using an image analysis system (Leica Q500MC, Qwin, UK). Prior to processing of the images, care was taken to assure that all pellets were detected as single entities. One pixel corresponds to 22 μm. All measurements were performed on 400 ± 50 particles. Eight Feret diameters were measured and the average Feret diameter calculated for each individual particle. Aspect ratio (longest Feret divided by its orthogonal Feret) was calculated for each individual particle; values for median and standard deviation were calculated.

2.6. Tensile strength of the pellets

Fifty pellets of each batch were crushed with a texture analyser (TA-XT2, Stable Micro Systems, UK) as described by Schröder and Kleinebudde [16]. The punch was moved

with a speed of 1 mm/s down on the pellet. The crushing strength (cs) was recorded as the force recorded for a strain corresponding to 50% of the pellet height (d). The tensile strength (ts) was calculated for each individual pellet as $ts = [4cs]/[\pi d^2]$. The average of 50 measurements was reported as the tensile strength for the batch.

2.7. Dissolution rate of the pellets

The in vitro dissolution was examined according to the paddle method (Ph. Eur). Samples of 100 mg pellets were exposed to two different test media (1000 ml 0.1 M HCl and 1000 ml phosphate buffer pH 6.8 Ph.Eur.) at 37 °C for 120 min at 50 rpm ($n = 3–6$). The method was slightly modified for pellets containing riboflavin: sample size 500 mg pellets and agitation 100 rpm.

Drug release was monitored spectrophotometrically (Shimadzu Photometer, UV-160A, Japan) and recorded for riboflavin at $\lambda = 445$ nm, for paracetamol at $\lambda = 243$ nm and for theophylline at $\lambda = 272$ nm. Quantification was based on standards.

2.8. SEM-micrographs of the pellets

The pellets were mounted on aluminium stubs using double-sided sticky tape sputter-coated with Au/Pd in combination 60:40 (Polaron E500 Sputter-coater, UK) and examined using a scanning electron microscope (JMS-6400 SEM, JEOL, Japan).

3. Results

3.1. Characteristics of pectinic acid

The raw material of pectinic acid (PA) as obtained from the producer was found to be almost insoluble in water; estimated solubility below 1:350 000 (Table 1). The pH of a 1% solution of the raw material was 3.28. Table 1 also presents the content of different elements in a fully hydrolysed sample of the raw material. The amount of barium, strontium and magnesium is below 0.5 μg/g. The content of iron was found to be 2 μg/g while the content of potassium approximately 22 μg/g and the content of calcium approximately 37 μg/g. Sodium was the element present at the highest concentration.

Table 1
Characteristics of pectinic acid

	% dissolved at max solubility[a]	Estimated solubility in water[a]	pH[a]				
Raw material	<0.000288	1 > 350 000	3.28				
	Content of element (μg/g pectinic acid)[b]						
	Ba	Sr	Mg	Fe	Ca	K	Na
Hydrolysed raw material[c]	0.21	0.47	0.21	2.05	36.7	21.3	750.0

[a] Determined in water at 25 °C.
[b] Determined by ICP-AES (corrected for content of elements in the solvent).
[c] Sample treated with 0.1 M NaOH (5 ml to 500 ml).

Table 2
Carbohydrate composition of pectinic acid determined by methanolysis/GC ($n = 3$, given as min and max value)

Type of carbohydrate	Content of carbohydrate mol%
Arabinose	0.5–0.6
Rhamnose	3.7–4.0
Xylose	0.9–1.1
Mannose	2.8–3.1
Galactose	6.7–7.5
Glucose	5.9–6.2
Glucuronic acid	7.0–7.7
Galacturonic acid	69.9–71.6

The carbohydrate composition of pectinic acid is shown in Table 2. The acidic monosaccharides (galacturonic and glucuronic acid) represented nearly 80 mol% of the PA. The content of rhamnose was found to be approximately 4 mol%. The remaining consisted of several neutral monosaccharides (arabinose, galactose, xylose, mannose and glucose).

3.2. Physical characteristics of the extrusion aiding excipients

Some physical characteristics of the excipients can be found in Table 3. The loss on drying for PA is higher than for MCC, but both values are below 10% wt. There is a small deviation in average particle size for the two excipients. The particle size distribution is slightly broader for the MCC than for PA.

3.3. Characteristics of the pellets

Pellets were successfully prepared both from pectinic acid and microcrystalline cellulose, but the process was found to be more sensitive to the amount of water required when using PA as an extrusion aid. At levels of granulation

Table 3
Physical characteristics of pectinic acid (PA) and microcrystalline cellulose (MCC)

Extrusion aid	Loss on drying[a] %	Particle size (μm)		
		D50	D90	D90 − D50
PA	8.0	69.6	141.0	71.4
MCC	3.4	88.9	178.3	89.4

[a] Determined after drying to constant weight in vacuum oven.

liquid close to the optimum, PA pellets showed a tendency to stick together during spheronisation. In order to produce pellets of optimal shape and size from PA, the spheronisation was performed under heating the double jacket of the spheroniser to 45 °C.

The shape and size of the resulting pellets were more sensitive to type and concentration of model drug for formulations based on PA than those with MCC (Fig. 1).

Spherical pellets resulted from both excipients for formulations containing 1% wt. riboflavin and 99% of

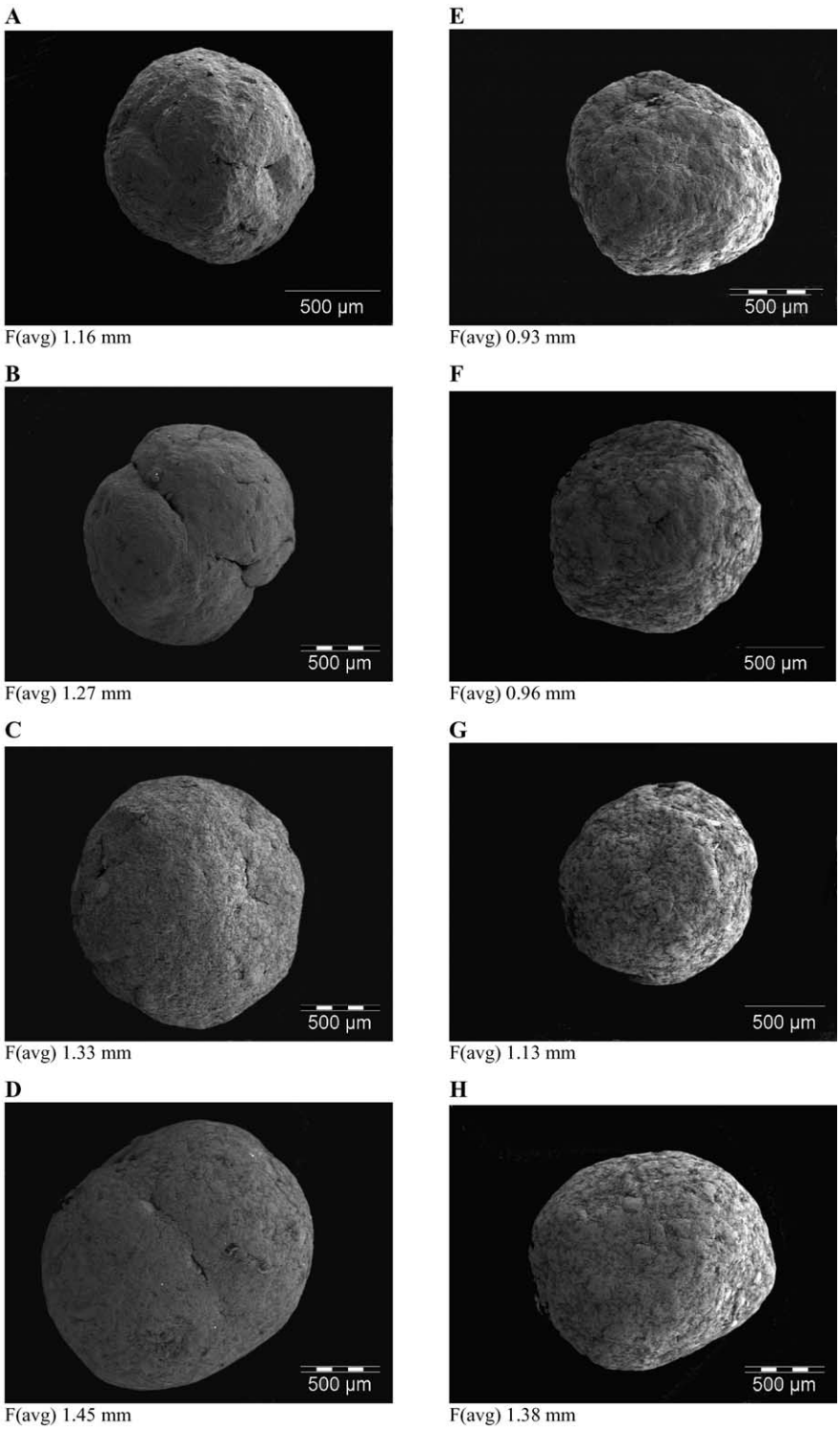


Fig. 1. SEM micrographs of corresponding pellets of pectinic acid (PA) and microcrystalline cellulose (MCC) with different type and concentration of model drug. (A) PA/riboflavin 99:1; (B) PA/theophylline 80:20; (C) PA/paracetamol 50:50; (D) PA/paracetamol 20:80; (E) MCC/riboflavin 99:1; (F) MCC/theophylline 80:20; (G) MCC/paracetamol 50:50; (H) MCC/paracetamol 20:80.

Table 4
Characteristics of pellets of pectinic acid (PA) and microcrystalline cellulose (MCC)

Excipient Type	Conc (%)	Model drug Type	Conc (%)	Water cont. LOD[a] (% ± S.D.)	Size and shape F_{avg}[b] (mm ± S.D.)	AR[c] (median ± S.D.)	Hardness ts[d] (N/mm^2 ± S.D.)
PA[e]	99	Riboflavin	1	131.6 ± 1.7	1.16 ± 0.11	1.04 ± 0.04	2.3 ± 0.83
PA[e]	80	Theophylline	20	108.5 ± 0.8	1.27 ± 0.14	1.09 ± 0.06	3.1 ± 1.23
PA[e]	50	Paracetamol	50	70.0 ± 0.8	1.33 ± 0.13	1.07 ± 0.04	1.3 ± 0.37
PA[e]	20	Paracetamol	80	35.7 ± 0.2	1.45 ± 0.14	1.14 ± 0.05	1.3 ± 0.27
MCC	99	Riboflavin	1	155.0 ± 0.5	0.93 ± 0.09	1.09 ± 0.07	29.4 ± 6.95
MCC	80	Theophylline	20	128.7 ± 1.6	0.96 ± 0.09	1.09 ± 0.05	12.8 ± 1.71
MCC	50	Paracetamol	50	90.5 ± 0.3	1.13 ± 0.12	1.08 ± 0.05	8.8 ± 1.03
MCC	20	Paracetamol	80	51.4 ± 2.7	1.38 ± 0.16	1.09 ± 0.17	8.9 ± 1.59

[a] Loss on drying after 24 h at 105 °C.
[b] Average Feret diameter.
[c] Aspect ratio.
[d] Tensile strength.
[e] Spheronized at 45 °C.

the extrusion aiding excipient. This is confirmed by aspect ratios below 1.1 for pellets of both excipients (Table 4). The average Feret diameter of the riboflavin pellets was larger for those with PA (1.16 mm) compared to those with MCC (0.93 mm). Higher levels of riboflavin were not investigated as this was regarded a model for low soluble drug substances administered in low doses.

Spherical pellets were also obtained for formulations containing up to approximately 80% wt. paracetamol. Pellets of PA containing 80% paracetamol were found to have an aspect ratio of 1.14 slightly deviating from a spherical shape while the corresponding MCC pellets is still below the aspect ratio of 1.1. Fig. 1D illustrates that the PA pellets are close to spherical but cracks developed during the shaping process indicate that the plasticity/rigidity ratio of the extrudate is not optimal.

Theophylline, however, seems to be a model drug that is less suited for combination with PA. Preparation of spherical pellets was found to be impossible for formulations of PA containing more than 20% wt. theophylline. For PA pellets containing 20% theophylline cracks could be observed (Fig. 1B), but the aspect ratio was still below 1.1. For pellets prepared from MCC there were no problems (Fig. 1F), even when increasing the theophylline content to more than 50% wt., an aspect ratio below 1.1 was still obtained.

The average Feret diameter is generally larger for PA pellets than for MCC pellets (Table 4) and reducing the amount of extrusion aiding excipients results in an increase in the average Feret diameter. The water content necessary to produce spherical pellets is higher for MCC formulations than for the corresponding PA formulations. The amount of water required for optimum properties of the extrudate is reduced as the amount of extrusion aiding excipients is reduced. The amount and solubility of drug substance also affects the required water content; low water-solubility of the drug requires higher amounts of water. Fig. 2 illustrates the range of moisture content investigated in order to produce pellets of formulations of PA and MCC (1 wt.% riboflavin). MCC is capable of forming short, nearly spherical pellets over a broader range of water content than PA. Reducing the amount of excipient narrows the range, most pronounced for PA. Above a certain water level aggregation during spheronisation could not be avoided for the PA formulation even by heating of the double jacket.

The tensile strength is higher for MCC formulations than for the corresponding PA formulations (Table 4). Different drug substances might also influence the pellet strength, but this effect is mixed with different levels of extrusion aid and is more difficult to interpret.

Fig. 3 presents the dissolution profiles obtained for pellets of PA and MCC in two dissolution media. In general it can be noticed that the dissolution rate is faster for pellets

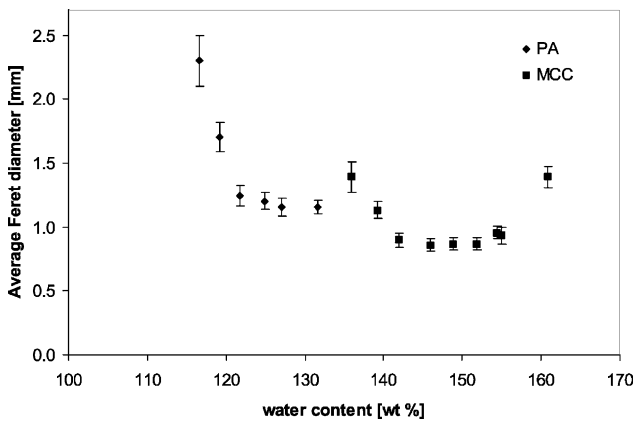


Fig. 2. Investigated range of moisture content of formulations of PA and MCC (1 wt.% riboflavin).

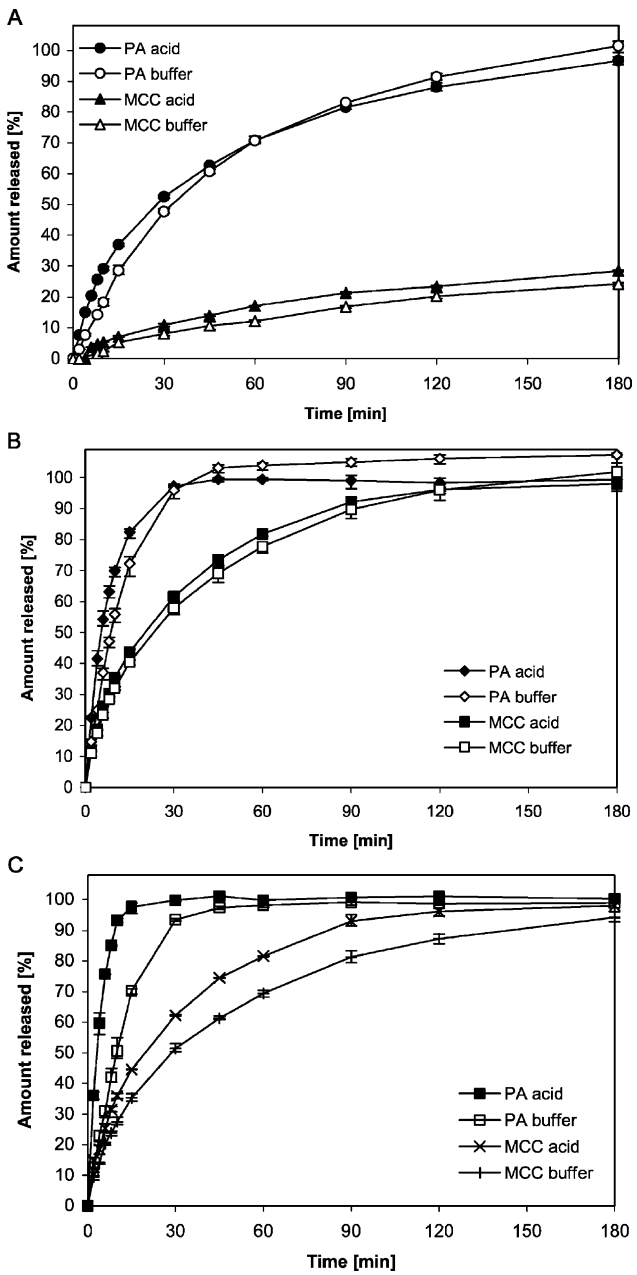


Fig. 3. In vitro dissolution profiles in 0.1 M HCl and phosphate buffer pH 6.8 comparing pellets prepared from pectinic acid (PA) and microcrystalline cellulose (MCC) ($n = 3$, error bars indicate max and min values. (A) Release of riboflavin from pellets of excipient/riboflavin 99:1; (B) release of paracetamol from pellets of excipient/paracetamol 20:80; (C) release of theophylline from pellets of excipient/theophylline 80:20.

of PA than the corresponding pellets of MCC. The difference is most pronounced for the low soluble riboflavin but the trend is seen for all model drugs. Both PA- and MCC-formulations containing 1% wt. riboflavin (Fig. 3A) and 80% wt. paracetamol (Fig. 3B) show a dissolution profile that seems to be independent of the test media while the dissolution profile for both types of excipients containing 20% wt. theophylline seems to be faster in a media of pH 1 than at pH 6.8.

For all PA pellets extensive fragmentation was observed during the first minutes of the dissolution testing. Formulations with a high fraction of model drug disintegrated completely. Fig. 4 shows SEM micrographs of MCC pellets prior to (Fig. 4A,B) and after 4 h of testing in phosphate buffer pH 6.8 (Fig. 4C,D). After the dissolution test of PA pellets only small fragments were left. The surface of MCC pellets containing riboflavin (99:1) did not show significant changes after the test. At higher drug concentrations (e.g. 20% theophylline), pores or holes can be observed in the MCC pellet where the water-soluble drug has been washed out during testing (Fig. 4D). At low excipient concentrations (20% extrusion and 80% paracetamol), even MCC pellets seems to fragmentize but the dissolution rate is still slower for MCC pellets compared to PA pellets (Fig. 3B).

4. Discussion

The overall conclusion of these studies is that pectinic acid is well suited as an extrusion aid for preparation of pellets with a fast drug release. The advantage of PA pellets over MCC pellets is the fragmentation and disintegration of the pellets on exposure to water resulting in a faster drug release. Preparation of spherical pellets (aspect ratio <1.1) with PA is more sensitive to the required amount of granulation liquid and to type and amount of drug substance than the conventional MCC pellets.

The reason for the suitable properties of pectinic acids in pelletisation by extrusion/spheronisation is that the substance is almost insoluble in water. Other pectins with higher solubility have been found to be less suitable [17]. Pectinic acid with a DM below 10% is described by the producer to be insoluble at pH values below 6–7 (Herbstreith and Fox, pamphlet). The solubility in water was estimated and found to be extremely low (1: $<$ 350 000). An intriguing question is why does a polymer with numerous hydrophilic groups appear to be insoluble in water? The pH of the solution indicates that the polycarboxylic acid is mainly on its acidic form, which is most hydrophobic and less water-soluble form. A possible explanation for the low water-solubility is that the polymer under these conditions has a conformation that protects the groups from hydration.

A well-known explanation to low solubility among pectin polysaccharides is of course cross-linking with calcium under formation of an insoluble complex [18]. In order to examine the possibility that the tested substance might be calcium-pectinate the content of several elements was measured. In addition to calcium other elements capable of forming ions with a valence of two or three could possibly be able to cross-link the pectin chains. The results of the ICP-AES analysis indicated that there are only very low contents of either of these elements (μg/g). In comparison, products purchased as calcium-pectinate contain in the order of magnitude 20 mg calcium per gram

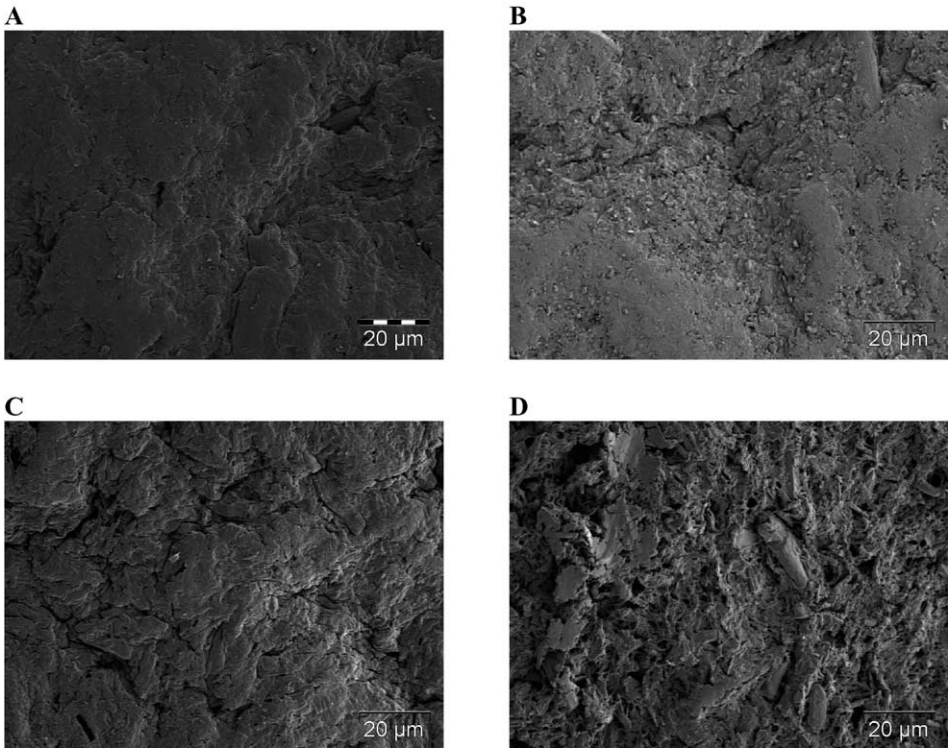


Fig. 4. SEM micrographs of pellet surfaces of microcrystalline cellulose before (A and B) and after (C and D) in vitro dissolution test for 4 h in phosphate buffer pH 6.8 (magnification 1000 ×). (A) MCC/riboflavin 99:1 (before); (B) MCC/theophylline 80:20 (before); (C) MCC/riboflavin 99:1 (after); (D) MCC/theophylline 80:20 (after).

pectin. Based on these finding it may be concluded that the insoluble substance is not likely to be a calcium-pectinate. The high content of sodium might be due to the hydrolysis of the raw material with NaOH prior to analysis.

The carbohydrate composition was as could be expected for a pectin derivative [19,20]. The main component was galacturonic acid, which is the main constituent of the PA backbone. The content of galacturonic acid was estimated to be approximately 70 mol%. It is known from the literature that the polygalacturonic acid is occasionally interrupted by rhamnose, creating kinks in the backbone [21]. The content of rhamnose was found to be approximately 4 mol%. The neutral monosaccharides (arabinose, xylose, mannose, galactose and glucose) are normally found in the side chains, also called the hairy regions, originating from the kinks introduced by rhamnose. The content of these monosaccharides is normally low. It is worth noticing that glucose could originate from contamination by any organic source as well as from the test material.

The physical characteristics of the two extrusion aiding excipients are in the same size range, and a comparison between the two is acceptable. The average particle size found for PA was 70 μm, which is intermediate between the selected PH102 (90 μm) and PH101 (50 μm) MCC quality. The flow properties of both extrusion aiding excipient were satisfying. Only at high concentrations of paracetamol fumed silica was required to improve the flow properties. As formulations of both excipients were treated equally this can be disregarded in the comparison between the two.

As suggested in the preliminary studies [14] an optimisation of shape and size of PA pellets could be accomplished by optimisation of the extrudate water content. Lactose previous used in the model system has successfully been replaced with different drugs and spherical pellets obtained. The ability of pectinic acid extrudate to retain water was inferior to that of the MCC extrudate. Aggregation occurred in the spheroniser for PA formulations at the required water levels. The phenomenon is caused by moisture disposal on the pellet surfaces causing them to stick together and to the walls during the process, and resulting in abortion of the spheronisation process. By heating the double jacket of the spheroniser to 45 °C the problem could be avoided and pellets with an appropriate aspect ratio could be prepared. The suitable range of moisture content for preparation of spherical pellets seems to be narrower for PA than for MCC.

Drug loads of up to 80% wt. are possible, thus it can be concluded that the extrusion aiding capacity of PA is high. However, PA is not as universally applicable as MCC. Experiments with one of the tested substances (theophylline) indicated that MCC was better suited, especially at high concentrations. With MCC it was possible to produce spherical pellets with 50% wt. theophylline whereas

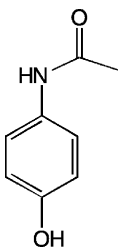
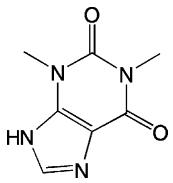
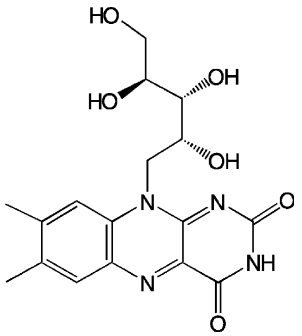
the maximal drug load of theophylline in PA pellets was 20% wt. Nevertheless, it seems like the properties of the drug substance it self are of greater importance when using PA as extrusion aid than with MCC.

PA used as an extrusion aid results in larger pellets than the corresponding formulation with MCC. Formulations with MCC require higher water content than PA in order to achieve the required plasticity/rigidity ratio and produce pellets with an aspect ratio below 1.1. It can be assumed that the amount of water required to obtain an appropriate plasticity/rigidity ratio is dependent on the solubility of the substances involved. Even though the solubility of PA has been estimated as very low, the solubility of MCC is even lower. This can also explain the fact that more water is required for formulations containing the highest amount of extrusion aid, namely those with the highest amount of insoluble substance. Another important factor in terms of required amount of water is the solubility of the drug. The low soluble riboflavin was found to require more water than the freely soluble paracetamol, which is in good agreement with reported findings in the literature [3,22].

Related to the water content is also shrinking during the drying process. Kleinebudde reported that pellets containing MCC tend to shrink during drying [23]. The extent of shrinking correlates to the amount of MCC in the formulation. This is in good agreement with the findings in the MCC formulations in this study. As the water content of PA pellets is lower than for MCC, the PA pellets would not be expected to shrink to the same degree as the MCC pellets. Pellets prepared from PA were found to have an average Feret diameter above the diameter of the dies (1 mm). A lower degree of shrinking might result in less dense, more porous pellets. The hardness of the MCC pellets was found to be approximately 10 times higher than that of the PA pellets. SEM micrographs also confirm more cracks or holes in the surface of PA pellets than on MCC pellets (Fig. 1).

The drug release from PA pellets is faster than from the corresponding MCC pellets regardless of type or concentration of model drug. This is primarily caused by the fragmentation of the PA pellets occurring shortly after exposure to test medium regardless of the pH. The MCC pellets remain intact in both media, except for formulations

Table 5
Physico-chemical characteristics of the different drugs (given in the literature)

Drug	Structural formula	MW	Solubility in water	pK_a	pH of a saturated aqueous solution
Paracetamol		151.2	1:70[a], 1:20[b]	9.5	5.1–6.5
Theophylline		198.2	1:120	8.8	6–7
Riboflavin		376.4	1:3000 to 1:20 000[c]	1.9 and 10.2	5.5–7.2

[a] Cold.
[b] Hot.
[c] Variation due to the variation in internal crystalline structure.

with very high drug loads. Formation of fragments were observed for MCC pellets containing 80% paracetamol, but even in this case the drug release from the corresponding PA system was faster. These findings suggest different drug release mechanisms from the two excipients. PA pellets with cracks or holes in the surface are easily subjected to water penetrating into the core of the pellets, thereby causing fragmentation and disintegration while MCC creates diffusion controlled systems. In addition PA has retained some of its swelling potential during the manufacturing process, causing rupture of the pellets and severe fragmentation followed by complete disintegration. MCC pellets, on the other hand, are reported not to retain their swelling potential after the manufacturing process [24], and will only disintegrate when the amount of drug is larger than the capacity of the MCC for keeping the structure together. At this point, when the drug has been dissolved, the structure will collapse and this could be observed as fragmentation, but is not a true disintegration. In MCC pellets with higher amounts of excipient, the water-soluble drug is washed out of the pellets leaving pores in the structure. This can be seen in the SEM micrographs in Fig. 4 where pores are found in the MCC pellets after the dissolution test, whereas for the PA pellets only a fine powder was left to examine.

The drug release rate is, as expected, depending on the solubility of the model drug. Riboflavin was selected to be a model of a drug with a very low solubility that is normally administered in low doses. The solubility of riboflavin depends on the crystal structure but is reported to be between 1:3000 and 1:20 000 (Table 5). As a model for a drug that is water-soluble and administered in high concentrations, paracetamol was chosen. The important observation is that the release rate was significantly increased from a disintegrating matrix like the PA pellets compared to the MCC pellets in all cases. Due to the very low water-solubility of riboflavin the test conditions were different (higher sample weights and faster speed) for these formulations compared to the other drug substances. In comparing the properties of the two extrusion aiding excipients this can be disregarded as both systems were treated equally.

It seems like PA as well as MCC behaves like a pH-independent excipient in the dissolution test. Both excipients show the same dissolution profile independent of the media for riboflavin- and paracetamol-containing pellets. With theophylline on the contrary, the drug release is faster in a media of pH 1 than at pH 6.8.

To summarise it can be stated that pectinic acid is well suited as an extrusion aiding excipient due to the low solubility of the raw material. The pelletisation properties are not as universal as for microcrystalline cellulose, but pectinic acid shows an advantage over microcrystalline cellulose in the formation of disintegrating pellets that allows a fast release of low soluble drugs.

Acknowledgements

We would like to express our gratitude to the companies Herbstreith and Fox GmbH, Germany and Pharmatrans Sanaq, Switzerland for the generous gifts of pectinic acid and microcrystalline cellulose, respectively. Special thanks are due to Dr Anne Berit Samuelsen, Department of Pharmacognosy, University of Oslo, Norway, for providing the working facilities for the methanolysis and GC of pectin, to Cand. Pharm. Christel Dolles Ørn, Weifa, Norway for providing the working facilities for particle characterisation and to Ms Anne-Marit Skramstad, Department of Analytical Chemistry, University of Oslo, Norway, for recording the ICP-AES data.

References

[1] I. Ghebre Sellassie, Pharmaceutical Pelletization Technology, Marcel Dekker, New York, USA, 1989.
[2] R.D. Shah, M. Kabadi, D.G. Pope, L.L. Augsburger, Physicomechanical characterization of the extrusion-spheronization process. 2. Rheological determinants for successful extrusion and spheronization, Pharm. Res. 12 (1995) 496–507.
[3] C. Lustig-Gustafsson, J.H. Kaur, F. Podczeck, J.M. Newton, The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation, Eur. J. Pharm. Sci. 8 (1999) 147–152.
[4] L. Baert, J.P. Remon, Influence of amount of granulation liquid on the drug-release rate from pellets made by extrusion spheronization, Int. J. Pharm. 95 (1993) 135–141.
[5] M. Schroder, P. Kleinebudde, Influence of formulation parameters on dissolution of propyphenazone pellets, Eur. J. Pharm. Biopharm. 41 (1995) 382–387.
[6] K.E. Fielden, J.M. Newton, R.C. Rowe, The influence of moisture-content on spheronization of extrudate processed by a ram extruder, Int. J. Pharm. 97 (1993) 79–92.
[7] H. Lindner, P. Kleinebudde, Use of powdered cellulose for the production of pellets by extrusion/spheronization, J. Pharm. Pharmacol. 46 (1994) 2–7.
[8] G.P. Millili, J.B. Schwartz, The strength of microcrystalline cellulose pellets—the effect of granulating with water ethanol mixtures, Drug Dev. Ind. Pharm. 16 (1990) 1411–1426.
[9] A.W. Basit, J.M. Newton, L.F. Lacey, Formulation of ranitidine pellets by extrusion-spheronization with little or no microcrystalline cellulose, Pharma. Dev. Tech. 4 (1999) 499–505.
[10] M.F.L. Law, P.B. Deasy, Effect of common classes of excipients on extrusion-spheronization, J. Microencaps. 14 (1997) 647–657.
[11] R. Junnila, P. Palviainen, J. Heinamaki, P. Myllarinen, P. Forssell, J. Yliruusi, Waxy corn starch: A potent cofiller in pellets produced by extrusion-spheronization, Pharma. Dev. Tech. 5 (2000) 67–76.
[12] E.I. Keleb, A. Vermeire, C. Vervaet, J.P. Remon, Continuous twin screw extrusion for the wet granulation of lactose, Int. J. Pharm. 239 (2002) 69–80.
[13] I. Tho, E. Anderssen, K. Dyrstad, P. Kleinebudde, S.A. Sande, Quantum chemical descriptors in the formulation of pectin pellets produced by extrusion/spheronisation, Eur. J. Pharm. Sci. 16 (2002) 143–149.
[14] I. Tho, S.A. Sande, P. Kleinebudde, Pectinic acid, a novel excipient for production of pellets by extrusion/spheronisation: preliminary studies, Eur. J. Pharm. Biopharm. 54 (2002) 95–99.

[15] A.B. Samuelsen, B.S. Paulsen, J.K. Wold, H. Otsuka, H. Yamada, T. Espevik, Isolation and partial characterization of biologically-active polysaccharides from plantago-major L, Phytother. Res. 9 (1995) 211–218.
[16] M. Schroder, P. Kleinebudde, Structure of disintegrating pellets with regard to fractal geometry, Pharm. Res. 12 (1995) 1694–1700.
[17] I. Tho, P. Kleinebudde, S.A. Sande, Extrusion/spheronisation of pectin based formulations. II. Effect of additive concentration in the granulation liquid, AAPS, Pharm. Sci. Tech. 2 (2001) 27.
[18] G.T. Grant, E.R. Morris, D.A. Rees, P.J.C. Smith, D. Thom, Biological interactions between polysaccharides and divalent cations: The egg-box model, FEBS Lett. 32 (1973) 195–198.
[19] M.A.V. Axelos, J.F. Thibault, J. Lefebvre, Structure of citrus pectins and viscometric study of their solution properties, Int. J. Biol. Macromol. 11 (1989) 186–191.
[20] A.G.J. Voragen, W. Pilnik, Pectins, in: A.M. Stephen (Ed.), Food Polysaccharides and their Applications, Marcel Dekker, New York, USA, 1995, pp. 287–339.
[21] H.A. Schols, E. Vierhuis, E.J. Bakx, A.G.J. Voragen, Hairy (Ramified) regions of pectins. Part IV. Different populations of pectic hairy regions occur in apple cell walls, Carbohydr. Res. 275 (1995) 343–360.
[22] G.A. Hileman, S.M. Upadrashta, S.H. Neau, Drug solubility effects on predicting optimum conditions for extrusion and spheronization of pellets, Pharm. Dev. Tech. 2 (1997) 43–52.
[23] P. Kleinebudde, Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties, Int. J. Pharm. 109 (1994) 209–219.
[24] P. Kleinebudde, Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: II. Swelling properties, Int. J. Pharm. 109 (1994) 221–227.