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Influence of the formulation composition on the in vitro characteristics of hot stage extrudates

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Abstract

The aim of this study was to evaluate the influence of the formulation composition on the characteristics of starch based hot stage extrudates in order to obtain high quality and high efficacy matrices for controlled drug delivery. Their characteristics were compared to those of a reference formulation, for which in vivo data were available. The influence of the starch type, the plasticizer and the lubricant were investigated. The extrudates were produced with a twin screw co-rotating extruder equipped with a twin screw powder feeder and a 3 mm cylindrical die. The extrudates were manually cut and dried for 48 h at 60°C prior to analysis. They were characterized by Karl Fischer titration, Hg-porosimetry, 4-point bending and dissolution testing. Changing the formulation composition did not affect the water content or the porosity of the extrudates but had an influence on their mechanical strength and dissolution profiles. These characteristics were particularly dependent on the plasticizer and lubricant concentration used and on the nature of the starch component and the lubricant. Expansion, depending on starch conversion and amylose–lipid complex formation, played a major role in the explanation of the results obtained. All the formulations tested showed a slow drug release profile in vitro. However, the differences with the reference formulation — which was tested in vivo in earlier work — were probably too small to give a distinct improvement of its in vivo behaviour.

Keywords: Hot stage extrusion; Starch; Sustained release matrix; Theophylline; In vitro

1. Introduction

During the last 10–15 years hot stage extrusion, a technique derived from the polymer and food industry (van Zuilichem, 1992), has been applied in the pharmaceutical industry to produce matrix formulations into which a drug is homogeneously embedded (Mank et al., 1989, 1990; Follonier et al., 1994, 1995; Gruenhagen, 1996; Sprockel et al., 1997). Both solid dispersions and solid solutions can be produced. The major advantage over the more conventional matrix production methods is the continuity of the production process as the different production steps (mixing, melting, homogenizing and shaping) are carried out in a single machine. This

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implicates a decrease in investment costs and an increased automation of the production. Furthermore no organic solvents have to be used during the production process, the technique offers a high throughput and low material loss and the products possess excellent homogeneity (Mueller et al., 1992; Breitenbach et al., 1995).

Starch was chosen as the matrix forming agent due to its low cost, high availability and non toxicity. Its excellent feasibility for hot stage extrusion has been established by a variety of applications in the polymer, food and agriculture technology (Launay and Lisch, 1983; Doane, 1992; Fritz and Widmann, 1993; Shogren et al., 1993; Carr et al., 1994; Krishnan et al., 1994; Schreiber et al., 1994). Although starch is widely used as a pharmaceutic aid, no literature is yet available regarding its possible application as a basic polymer for the production of hot stage extruded drug/matrix formulations.

In a first paper the in vivo behaviour of a starch based hot stage extrusion formulation consisting of 53% corn starch, 15% sorbitol, 30% theophylline monohydrate and 2% glyceryl monostearate was evaluated (Henrist et al., 1999). It was concluded that the drug release from the experimental formulation was retarded but was still faster than that observed for the commercially available sustained release system Xanthium®. Therefore it was the objective of this paper to investigate if the drug release and other extrudate characteristics could be affected by changes in formulation composition. Our final goal was to achieve high quality and high efficacy starch based hot stage extruded matrices for controlled drug delivery.

2. Materials and methods

2.1. Materials

Starches and sugar alcohols were received from Eridania Béghin Say Cerestar (Vilvoorde, Belgium). Potato starch, corn starch, rice starch and wheat starch have approximately the same amylose-amylopectine ratio (25/75) but a different botanical origin and different granule dimensions with respective maximal values of 100, 32, 20 and 45 μm. The sugar alcohols sorbitol, xylitol and lactitol have a similar melting point (around 95°C), but different water solubilities (at 20°C) of, respectively, 235, 169 and 125% (w/w) whereas erythritol, maltitol and xylitol have a water solubility (at 20°C) of around 160% (w/w) but different melting points of 121, 150 and 94°C, respectively. Two sorbitols with a different particle size distribution were used (sorbitol P6 with a particle size ≤ 250 μm and sorbitol P3 with a particle size between 250 and 1000 μm). Theophylline monohydrate was purchased from Ludeco (Brussels, Belgium). Glyceryl monostearate was obtained from Mosselman (Brussels, Belgium). Sucrose stearates with HLB-values of 2, 9 and 16 were supplied by Mitsubishi-Kasei Food Corporation (Tokyo, Japan) and fatty acids with chain lengths of 16, 18 and 22 C-atoms (palmitic, stearic and behenic acid) were obtained from Unichema International (Gouda, the Netherlands).

2.2. Production process

Prior to hot stage extrusion, the different components of the formulation were premixed in a Hobart A 200 planetary mixer (Kampenhout, Belgium). A reference mixture was used which consisted of 53% corn starch, 15% sorbitol as a plasticizer, 30% theophylline monohydrate and 2% glyceryl monostearate as the lubricant. All of the formulations tested differed in one aspect only from the reference mixture: either one constituent was replaced by another or the quantitative composition was modified. In this way the influence of the following parameters on the in vitro extrudate characteristics was investigated: the influence of the botanical origin and the degree of gelatinization of the starch; the influence of the solubility, melting point, particle size and percentage of the plasticizer and the influence of the HLB-value, the chain length and the percentage of the lubricant (Table 1).

The extrusion was performed on a MP 19 TC 25 laboratory scale co-rotating twin screw extruder of APV Baker (Newcastle-under-Lyme, UK). The machine was equipped with a control

panel (for the installation and/or control of the barrel and melt temperatures, the screw speed, the powder feed rate, the die pressure and the torque), a standard screw profile with two mixing sections, a 3-mm cylindrical die, a twin screw powder feeder and a peristaltic pump connected to the first barrel zone of the extruder. The pump was used for the addition of water, acting as a plasticizer, during the extrusion.

The following extrusion conditions, based on preliminary research work, were used: a screw speed of 200 rpm, a powder feed rate of 2.4 kg/h and a water addition rate of 0.6 kg/h. The following temperature profile was installed: 60–90–100–100–80°C from the powder feeder to the die. The effective temperatures equalled the installed temperatures except for the die zone where the effective temperature was higher (95°C) than installed since the experiments were performed without cooling system.

The extrudates were cut into pieces of approximately 10 cm and prior to further analysis they were oven dried at 60°C for 48 h.

2.3. Characterization of the extrudates

The moisture content of the extrudates was determined using a Mettler DL35 Karl Fischer titrator (Mettler-Toledo, Beersel, Belgium) in combination with a Mettler DO337 oven. The extrudates were cut in small pieces and placed in a Pyrex vessel inside the oven operated at 200°C.

Table 1
Composition of the powder mixtures in the different experiments [a]

Mixture	Starch component	Drug	Plasticizer	Lubricant
Reference	53% Corn starch	30% TM	15% sorbitol P6	2% GMS
Influence of the starch type				
1	53% Rice starch	R	R	R
2	53% Potato starch	R	R	R
3	53% Wheat starch	R	R	R
4	53% Pregelatinized starch	R	R	R
Influence of the plasticizer type				
5	R	R	15% xylitol	R
6	R	R	15% lactitol	R
7	R	R	15% erythritol	R
8	R	R	15% maltitol	R
9	R	R	15% sorbitol 500–1000 μ	R
10	R	R	15% sorbitol 250-500 μ	R
Influence of the percentage plasticizer in the formulation				
11	68% Corn starch	R	0% sorbitol P6	R
12	60.5% Corn starch	R	7.5% sorbitol P6	R
13	38% Corn starch	R	30% sorbitol P6	R
Influence of the lubricant type				
14	R	R	R	2% Sucrose stearate HLB2
15	R	R	R	2% Sucrose stearate HLB9
16	R	R	R	2% Sucrose stearate HLB16
17	R	R	R	2% Palmitic acid (C16)
18	R	R	R	2% Stearic acid (C18)
19	R	R	R	2% Behenic acid (C22)
Influence of the percentage lubricant in the formulation				
20	55% Corn starch	R	R	0% GMS
21	54% Corn starch	R	R	1% GMS
22	51% Corn starch	R	R	4% GMS

[a] R = as in the reference mixture; TM = theophylline monohydrate; GMS = glyceryl monostearate.

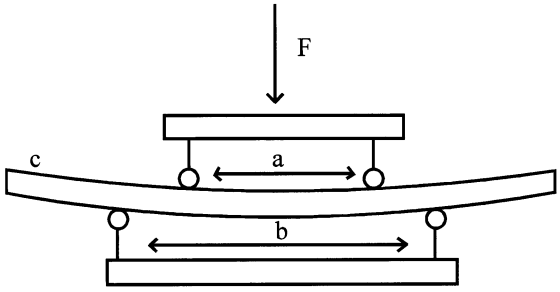

Fig. 1. Schematic view of the position of the test specimen in relation to the points of support and points of power application in the 4-point bending test with F = load, a = distance between the two points of power application (42 mm), b = distance between the two points of support (80 mm) and c = test specimen.

For 15 min the evaporated water was transported by a nitrogen stream of 300 ml/min from the sample vessel to the reaction medium. Afterwards the water was titrated with Hydranal® Composite 5 (Riedel-de Haën, Seelze, Germany) with a theoretical titre of 5 mg H_2O/ml. The analysis was performed three times.

The mechanical strength of ten samples of approximately 10 cm length was evaluated using a 4-point bending test performed on a Lloyd 1000 R tensile testing machine (Lloyd Instruments, Fareham, England) with a load cell of 20 N and a cross head speed of 1 mm/min. The samples were placed on the points of support in a way that their midpoints fell together with the midpoint between the two points of support and the two points of application of the load (Fig. 1). The test was automatically stopped when break was detected. The maximum load at break was used to calculate the maximum tensile strength (σ_{max}) for those samples which broke between the two points of application of the load. The following formula, derived from the theory of Timoshenko (1955) was applied:

$$\sigma_{max} = (4Qx)/(\pi r^3)$$

where Q is the load at one point of application, x the distance between point of support and point of application of the load and r the radius of the cylinder at the point of break.

The results were presented as a mean value. The radius of the extrudates was the average of ten values. Each value was the average of four measurements performed with an electronic digital caliper (Bodson, Liège, Belgium). The measurements took place during the 4-point bending tests and it were the radii of the different samples at the point of break, measured at two positions on each part of the broken cylinders.

The porosity was measured in duplicate by means of an Autopore III 9410 mercury porosimeter (Micromeritics, Zaventem, Belgium). A calibrated solids penetrometer with a 5 ml sample vessel and a 0.38 ml stem was therefore used.

Two dissolutions per formulation were performed in a VK 7000 dissolution system with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA) at 37 ± 0.5°C and 100 rpm using the paddle method (Eur. Ph.). Two different media with $\mu = 0.308$ were used: a 0.2922 M KCl solution brought to a pH of 1.8 with HCl and a 0.0835 M Na_3PO_4 solution brought to a pH of 7.5 with HCl. The dissolutions were performed on six samples of approximately 3 cm. Samples were taken after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. After appropriate dilution they were measured at 272 nm by means of a Perkin Elmer Lambda 12 UV-vis double beam spectrophotometer (Zaventem, Belgium). The theophylline monohydrate concentrations were calculated from a calibration curve between 0 and 0.025 g/l. To compare the dissolution profiles, AUC values were calculated from the dissolution profiles with the trapezoidal method. The AUC was determined between 0 and 8 h as the drug release at this last time point was between 70 and 90% (Anderson et al., 1998). When the AUC would have been measured on the total profile, differences in the first part of the dissolution curves could have been levelled out.

3. Results and discussion

3.1. Preliminary tests

Hot stage extrusion has proven to be a successful technique in the polymer and the food indus-

try and the excellent feasibility of starch as processing polymer has been established by a wide variety of applications in these fields. The choice of the reference mixture for this research work is based on the experience and findings in the food technology (De Bock et al., 1993, 1994). Two additives were included in the mixture to increase the ease of manufacturing: sorbitol was chosen as a plasticizer and glyceryl monostearate as a lubricant in an amount of 15 and 2% (w/w) based on the dry mixture, respectively. The water addition was fixed to 20% (w/w) based on the wet mass. Drug loadings between 0 and 50% caused no problems during the extrusion process and extrudates of good visual quality were produced. In the experiments described here a drug loading of 30% was used. The reference extrusion process was determined empirically since the extrusion parameters are not only dependent on the processed formulation, but also on the type of extruder used.

The in vivo behaviour of the above described experimental extrusion formulation (reference mixture) was evaluated in a randomized crossover design study with the commercially available sustained release system Xanthium® as the second formulation (Henrist et al., 1999). The experimental formulation exhibited low to moderate sustained release properties, but performed less well in comparison to Xanthium®. Therefore it was the objective of this paper to investigate if the drug release and other extrudate characteristics could be modified by changing the formulation composition in order to obtain better matrices for controlled drug delivery.

3.2. Extrusion behaviour

No problems were experienced during the extrusion process. The extrudates were of good visual quality and were homogeneous which is shown by the low standard deviations on the AUC values from the dissolution profiles of six independent samples (Table 2).

3.3. Extrudate characteristics

3.3.1. General considerations

The obtained data from the characterization tests of the reference extrudates are shown in Table 2. The coefficients of variation are below 5% for every test but the tensile strength measurements, where it is still lower than 10%. The standard deviations and coefficients of variation presented in Table 2 are representative for the other extrusion experiments.

During the extrusion of the different powder mixtures the average radius of the dried extru-

Table 2
Characterization results of the reference extrudates

	Water content (%)	Porosity (%)	Tensile strength (N/mm^2)	AUC pH 1.8 (%h)	AUC pH 7.5 (%h)	Radius (mm)
1	4.69	5.93	22.95	410.8	412.1	1.464
2	4.46	5.74	24.42	421.3	403.8	1.4575
3	4.39		23.80	399.8	401.9	1.455
4			19.40	390.3	403.9	1.466
5			19.33	395.6	420.3	1.561
6			20.40	417.7	415.9	1.544
7			20.54			1.57
8						1.5775
9						1.484
10						1.4625
Mean	4.51	5.84	21.6	406	410	1.50
S.D.	0.157		2.12	12.6	7.6	0.052
C.V. (%)	3.48		9.86	3.09	1.85	3.46

dates did not always equal the die radius of 1.5 mm. In some cases the extrudate radius was smaller due to shrinkage, in other cases it was larger due to expansion (the most extreme examples were formulations 2 (2 mm) and 13 (1.31 mm)).

Expansion of starch containing extrudates at the extruder die is a phenomenon intensively investigated in the domain of the food technology (Launay and Lisch, 1983; Chinnaswamy and Hanna, 1988a,b,c, 1990; Sokhey et al., 1994; Fan et al., 1996). Among the variables that govern expansion (extruder barrel temperature, screw speed, die design, screw design, moisture content of the feed material, starch composition, lipid and protein content, presence of sugars), only those concerning the composition of the extrusion mixtures could contribute to the expansion or shrinkage seen in our experiments, since each extrusion was performed under the same process conditions. At fixed temperature and water content, substances that can alter the specific mechanical energy (SME) during extrusion and the residence time in the extruder, have an influence on the starch gelatinization. Sugars, for example, decrease the SME due to a lowering of T_g. This results in less starch conversion and less expansion (Fan et al., 1996). However, expansion not only depends on starch conversion. Lipids can inhibit expansion through amylose–lipid complex formation (Chinnaswamy and Hanna, 1988b). This complex formation occurs in the presence of amylose and lipids such as fatty acids and monoglycerides and has already been observed during the hot stage extrusion process (Colonna and Mercier, 1983; Galloway et al., 1989; Bhatnagar and Hanna, 1994a,b). Some remarkable effects of these complexes are an increase of the density and a decrease of the expansion and swelling ability of the final product (Bhatnagar and Hanna, 1994a).

In conclusion it can be stated that during melt extrusion of starch containing mixtures, expansion results from the competition between starch conversion and amylose–lipid complex formation and that these phenomena play a major role in the explanation of the extrudate characteristics.

3.3.2. Water content, porosity and mechanical strength

In all experiments the water content after drying was between 2.3 and 5.9% (Table 3). The porosity of the extrudates varied from 5.5 to 7.8% (Table 3).

With regard to the mechanical strength of the extrudates, it has to be mentioned that with formulations 11 and 13 it was impossible to carry out the 4-point bending test. This was due to a high brittleness and a lack in stiffness of the extrudates, respectively. From the results of the 4-point bending test it can be concluded that matrices with a smaller and higher radius than the reference extrudates were generally stronger (Table 3). In the first case the amylose–lipid complexes reinforced the extrudates. In the second case, the improved mechanical strength of the extrudates had to be of another, yet unknown origin. In both cases there were however exceptions, which brings along a problem that was experienced with the 4-point bending characterization test. Starch conversion and the degree of complex formation have an influence on the expansion and consequently on the thickness of the extrudates. Since the maximum tensile strength depends on the average radius of the tested extrudates, care should be taken when interpreting the results, as the extrudates are not of a similar thickness. Consequently the calculated maximum tensile strength does not only reflect the mechanical strength of the matrix itself, but also differences in extrudate dimensions.

3.3.3. Dissolution behaviour

Concerning the dissolution behaviour of the extrudates the conclusion can be drawn that in all cases the drug release was retarded, and pH and ionic strength independent. A slower drug release in comparison to the reference formulation was obtained when potato starch was used instead of corn starch (formulation 2), when sucrose stearate with a HLB-value of 2 and behenic acid with a chain length of 22 carbon atoms were used as lubricants instead of glyceryl monostearate (formulations 14 and 19), in the absence of a lubricant (formulation 20), with 1% glyceryl monostearate as a lubricant (formulation 21) and

Table 3
Mean results of the different extrusion experiments [a]

Experiment (cf. Table 1)	Water content (%)	Porosity (%)	Tensile strength (N/mm^2)	AUC pH 1.8 (%h)	AUC pH 7.5 (%h)	Radius (mm)
Reference	4.5	5.8	21.6 ($n=7$)	406	410	1.50
1	4.7	6.8	26.9 ($n=5$)	482	n.a.	1.32
2	5.8	5.5	26.7 ($n=4$)	314	316	2.00
3	4.8	6.5	22.1 ($n=8$)	389	385	1.61
4	4.1	6.9	25.0 ($n=6$)	454	436	1.37
5	3.4	n.a.	28.8 ($n=6$)	410	393	1.51
6	5.2	n.a.	21.2 ($n=10$)	394	396	1.52
7	3.4	7.0	22.6 ($n=6$)	405	427	1.53
8	4.7	6.9	19.5 ($n=10$)	440	416	1.48
9	4.1	6.1	23.6 ($n=6$)	405	398	1.53
10	4.8	n.a.	21.7 ($n=7$)	375	366	1.63
11	2.3	5.9	n.a.	642	639	1.85
12	4.5	7.2	33.7 ($n=10$)	353	346	1.65
13	3.4	7.8	n.a.	571	542	1.31
14	5.9	6.1	21.4 ($n=6$)	334	341	1.76
15	4.0	6.5	30.4 ($n=7$)	385	378	1.59
16	4.4	6.9	28.5 ($n=10$)	397	399	1.51
17	4.5	6.5	24.4 ($n=5$)	423	420	1.46
18	4.4	6.6	23.4 ($n=6$)	401	n.a.	1.48
19	5.6	6.0	20.6 ($n=9$)	344	347	1.72
20	4.7	5.8	37.9 ($n=4$)	330	324	1.74
21	4.5	5.6	29.7 ($n=4$)	352	363	1.59
22	4.2	7.0	24.9 ($n=8$)	433	500	1.43

[a] n.a., No value available

when 7.5% sorbitol was used as the plasticizer instead of 15% as in the reference formulation (formulation 12). An example is shown in Fig. 2. In all the above mentioned cases expansion was promoted either through a higher degree of starch conversion or a lower degree of complex formation. As a consequence the drug diffusional path became longer during the dissolution and so the drug release slower. In the case of behenic acid and sucrose stearate with HLB 2 used as lubricants the lower degree of complexation was caused by the size and the molecular weight of the lipid molecule: a higher number of carbon atoms in the fatty acid chains and more fatty acid chains in the lubricant molecule, made the complex formation more difficult (Bhatnagar and Hanna, 1994a). In the absence of a lubricant in the formulation it was obvious that complex formation was only possible with the small amount of naturally occurring lipids present in starch. When only 1% of lubricant was used, less complexes were formed than with 2% of lubricant as in the reference formulation. When 7.5% sorbitol was used as a plasticizer relatively more starch was used in the formulation compared to the reference composition and it is known that expansion is promoted, when the amount of starch is raised (Chinnaswamy and Hanna, 1988b). Furthermore the percentage of sugar was decreased in comparison to the reference formulation, resulting in a higher SME during extrusion and consequently a higher degree of starch conversion, which in turn increased the expansion (Fan et al., 1996).

A faster drug release than for the reference formulation was observed when rice starch and pregelatinized starch were used (formulations 1 and 4), in the absence of a plasticizer (formulation 11), with 30% plasticizer instead of the 15% as in the reference mixture (formulation 13) and with 4% of the reference lubricant in the mixture (for-

mulation 22). An example is shown in Fig. 2. Complex formation was promoted and consequently expansion inhibited, when 4% lubricant was used due to a higher amount of lubricant present in the formulation. The reason of the faster drug release in the absence of plasticizer was not evident. In the absence of a plasticizer more starch was used in the formulation and normally this should result in an increased expansion and a slower drug release. Probably the faster drug release seen with the formulation without plasticizer was due to the fact it disintegrated during dissolution testing. When 30% plasticizer was used in the formulation less starch was present in the mixture and consequently less expansion could take place (Chinnaswamy and Hanna, 1988a). In addition, more sugar was present in the formulation, which decreased the SME during the extrusion and as a consequence the degree of starch conversion and the expansion (Fan et al., 1996).

All other formulations showed approximately the same drug release profile as the reference formulation. Mixture 3, 16 and 18 behaved as expected since wheat starch and corn starch have similar granule dimensions and since a fatty acid and its corresponding monosubstituted lipid show a similar degree of amylose–lipid complex formation (Bhatnagar and Hanna, 1994a).

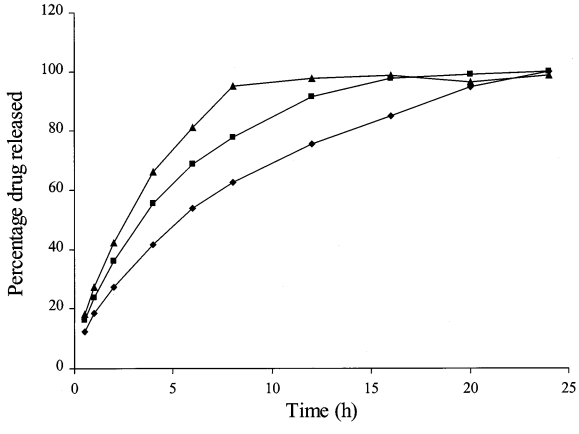

Fig. 2. Comparison between the dissolution profiles of the reference formulation containing corn starch (■), formulation 1 containing rice starch (▲) and formulation 2 containing potato starch (◆) in the buffer medium at pH 1.8. All formulations contained 30% theophylline monohydrate.

It is clear that it is possible to change the drug release from starch based hot stage extruded matrix formulations by modifying the formulation composition. However, the differences in comparison to the reference dissolution profile are probably too small to change also the in vivo performance of these formulations.

4. Conclusions

Hot stage extrusion of starch based formulations is a promising new pharmaceutical technique for the production of matrix formulations.

Changing the composition of the formulation did not affect the water content or the porosity of the extrudates but did have an influence on their mechanical strength and their dissolution profiles. These two characteristics were much dependent on the percentage plasticizer and lubricant used and on the nature of the starch component and lubricant. Expansion, depending on starch conversion and amylose–lipid complex formation, played a major role in the explanation of the results obtained. All the formulations tested showed a slow drug release profile in vitro. However, the differences with the reference formulation were probably too small to lead to an in vivo behaviour superior to that of the reference formulation.

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