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Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug

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Abstract

The influence of different formulation and process parameters on the characteristics of lyophilized oral dosage forms was investigated. Maltodextrins, gelatins, xanthan gum and hydroxyethylcellulose were evaluated as excipients in the formulation of freeze-dried tablets. The resulting tablets were analysed for mechanical strength, porosity, disintegration time and residual moisture. Scanning electron micrographs of the fracture plane of the tablets were taken. Additionally dissolution tests were performed on lyophilized tablets containing hydrochlorothiazide as a model drug. The concentration of the maltodextrins, used as the matrix forming agent, influenced the integrity and strength of the tablets. Increasing the maltodextrin concentrations resulted in stronger tablets. The concentration of the maltodextrins had also an influence on the pore size of the freeze-dried product. There was no influence of the DE value of the maltodextrin on the characteristics of the tablets. The disintegration time of the tablets was also affected by the maltodextrin concentration. The strength of the tablets depended on the xanthan gum concentration and the tablet dimensions. Compared to the formulations using xanthan gum as a binder in the same concentration, the disintegration time of the tablets containing hydroxyethylcellulose (HEC) was much shorter: 55 s for the xanthan gum formulations and 7 s for the HEC formulations. The in vivo disintegration time was significantly higher at 0.5% (w/v) HEC compared to 0.25% (w/v) ($P < 0.01$). The in vivo disintegration time of the tablets containing hydrolysed gelatin Solugel® LB as a binder was below 23 s for the in vivo tests. Unlike the xanthan gum formulations, no gel-like structure was formed upon contact with the saliva. The strength of the tablets was enhanced by using higher maltodextrin concentrations. The incorporation of hydrochlorothiazide in the formulations induced a decrease in strength of the tablets. The percentage of HCT released within 10 min was $64.55 \pm 2.87\%$ and $77.84 \pm 8.94\%$ for the reference tablets and the lyophilized tablet formulation, respectively. The addition of PEG 6000 (1% w/v) resulted in an increase of drug release as 93.3% was released from the lyophilized tablets within 10 min. However, the incorporation of PEG 6000 in the formulation resulted in a decrease in the strength of the tablets. © 1997 Elsevier Science B.V.

Keywords: Lyophilisation; Rapidly disintegrating tablets; Maltodextrin

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Table 1
Composition of some selected tablets (15 mm) on a dry weight base

Solutions (%; w/v)			Tablet		
			Theoretical weight (mg; w/w)		Weight after lyophilization (mg)
1	Maltodextrin DE12	5	Maltodextrin DE12	40	48 ± 3
	Xanthan gum	0.5	Xanthan gum	4	
2	Maltodextrin DE12	10	Maltodextrin DE12	80	89 ± 2
	Xanthan gum	0.5	Xanthan gum	4	
3	Maltodextrin DE12	20	Maltodextrin DE12	160	172 ± 4
	Xanthan gum	0.5	Xanthan gum	4	
4	Maltodextrin DE24	10	Maltodextrin DE24	80	101 ± 3
	Solugel LB	2	Solugel LB	16	
5	Maltodextrin DE38	20	Maltodextrin DE38	160	166 ± 3
	HEC	0.25	HEC	2	
6	Maltodextrin DE38	20	Maltodextrin DE38	160	224 ± 6
	Xanthan gum	0.5	Xanthan gum	4	
	HCT	1.25 g	HCT	50	
	Deionized water	to 20ml			

1. Introduction

Most pharmaceutical dosage forms for oral administration are formulated to be swallowed or chewed in order to deliver the drug. Pediatric and geriatric patients may have difficulties swallowing or chewing these tablets. Tablets that rapidly dissolve upon contact with saliva in the buccal cavity could present a solution to those problems and so there is an increased interest in fast dissolving dosage forms for buccal, sublingual and oral administration. Oral lyophilized products combine the properties of freeze-dried dosage forms as fast reconstitution, good preservation and stability, with the benefits of liquid dosage forms for bioavailability (Jaccard and Leyder, 1985).

In this study, the influence of different formulation and process parameters on the characteristics of lyophilized oral dosage forms was investigated. Maltodextrins, gelatins, xanthan gum and hydroxyethylcellulose were evaluated as possible excipients in the formulation of freeze-dried tablets. Additionally dissolution experiments were performed using hydrochlorothiazide (HCT) as a model drug. HCT was chosen as a poorly soluble drug because the objective was to look at the influence of structure disruption of lyophilised tablets in the presence of 'suspended' material.

2. Materials and methods

2.1. Materials

The spray dried maltodextrins (Eridania-Beghin Say-Cerestar, Vilvoorde, Belgium) were obtained by enzymatic hydrolysis of corn starch, and had different dextrose equivalents (D.E.): C(PUR01910 (D.E. = 14), C(PUR01921 (D.E. = 22), C(PUR01934 (D.E. = 38). Xanthan gum (Ludeco, Brussels, Belgium) and Idroramnosan® (hydroxyethylcellulose 2% w/v: 5800 mPa.s) (Ludeco, Brussels, Belgium) and different gelatins (PB Gelatins, Vilvoorde, Belgium): hydolysed gelatins Solugel® LB (Bloom value 10–30 g) and Solugel® P (Bloom value 0 g) and Cryogel 220–400 (Bloom value 220 g) were evaluated as binding agents. All the gelatins were cold water soluble. Polyethyleneglycol (PEG 6000) was obtained from Union Carbide (Danbury, Connecticut, US). Solutions were made in destilled water.

Karl Fischer reagents used were Hydranal Composite 5 and dried methanol (Riedel-de-Haen, Seelze, Germany).

Hydrochlorothiazide (Batch no. B; Ludeco, Brussels, Belgium) was chosen as a model drug. HCT is a diuretic, practically insoluble in

Table 2
Evaluation of freeze-dried tablets (15 mm) based on the combination of maltodextrins and xanthan gum

Formulation	Disintegration time (s)	Strength (N)		Residual Moisture (%)
	In vivo	Maximum load (N)	Maximum force (N)	
Maltodextrin				
DE12				
5% w/v	10 ± 3^{b}	4.6 ± 2.1	0.63 ± 0.12	6.83 ± 0.51
10% w/v	55 ± 5^{c}	10.2 ± 3.2^{c}	1.48 ± 0.21^{d}	5.36 ± 0.31
20% w/v	61 ± 6^{c}	$15.3 \pm 4.1^{c,d}$	2.85 ± 0.22^{a}	4.46 ± 0.22
DE 24				
5% w/v	32 ± 3	4.4 ± 1.2	0.53 ± 0.15	6.23 ± 0.58
10% w/v	31 ± 2	6.5 ± 2.1	1.31 ± 0.31^{d}	6.31 ± 1.21
20% w/v	47 ± 9^{a}	8.6 ± 2.3^{d}	2.88 ± 0.53^{a}	5.63 ± 0.89
DE 38				
5% w/v	33 ± 4	4.8 ± 3.2	0.50 ± 0.14	6.59 ± 1.21
10% w/v	34 ± 5	7.2 ± 2.1	1.33 ± 0.15^{d}	6.16 ± 0.35
20% w/v	46 ± 1^{a}	11.1 ± 1.6^{d}	2.76 ± 0.61^{a}	5.78 ± 0.68

A concentration of 0.5% (w/v) xanthan gum was used in all formulations.
All results are presented as mean $\pm$ S.D.; $n = 5$.
[a]Significaltly higher than 5% (w/v) and 10% (w/v) ($P < 0.05$).
[b]Significantly lower than DE24 and DE38, same concentration ($P < 0.05$).
[c]Significantly higher than DE24 and DE38, same concentration ($P < 0.05$).
[d]Significantly higher than 5% w/v, same DE value ($P < 0.05$).

water (25°C) and having a solubility of 250 mg/l in 0.1 N HCl (25°C).

2.2. Methods

2.2.1. Preparation of the tablets

Solutions were prepared containing maltodextrins in a concentration range 5–20% (w/v) in combination with xanthan gum, hydroxyethylcellulose (HEC) and gelatins in a concentration range 0.1–2% (w/v), 0.25–0.5% (w/v) and 0.1–3% (w/v), respectively. A volume of 800 l and 400 l, respectively was filled in PVC blisters with a diameter of 15 mm, 10 mm respectively. The blisters had a depth of 6 mm. In the formulations containing HCT, 1.25 g of the drug was suspended in 20 ml of the respective solution and 800 l of the suspension was filled in PVC blisters and resulted in a HCT dose of 50 mg per tablet. The blisters were placed on the shelves of the freeze-dryer (Amsco-Finn Aqua GT4, Amsco, Brussels, Belgium). The samples were frozen to 228 K at a rate of 0.5 K min^{-1} or 10 K min^{-1} and were kept at this temperature for 1.5 h. Primary drying was performed by keeping the blisters for 8 h at a pressure of 1 mbar, a shelf temperature of -258 K and a condensor temperature of 213 K. Secondary drying was carried out by reducing the pressure to 0.1 mbar and increasing the shelf temperature to 298 K. Secondary drying time was 6 h. Lyophilisation was terminated by venting the drying chamber with air.

The composition of the tablets on a dry weight basis is presented in Table 1.

2.2.2. Scanning electron microscopy

Scanning electron micrographs of the fracture plane of the tablets were taken using a XL3 Scanning Electron Microscope (Philips, Eindhoven, The Netherlands).

2.2.3. Porosimetric analysis

The size of the tablets was determined using mercury porosimetry (AutoPore III 9420 System, Micromeretics Instrum. Corp., Norcross,

GA, USA). Results are presented as a mean median pore diameter (volume) ± S.D. ($n = 3$).

2.2.4. Mechanical strength testing

A tensile testing machine (type L1000R, Lloyd Instruments, Segentworth, Fareham, UK), equipped with a 20 N load cell was used to determine the tablet strength. The tablet was attached vertically to a lower aluminium support with cyanoacrylate glue (Loctite Super Glue gel, Loctite Belgium, Kontich, Belgium). The superior cross sectional bar with the crosspiece was then lowered at a crosshead speed of 50 mm min^{-1} and 20 mm min^{-1} for the 15 mm and 10 mm diameter tablets, respectively. A load (N) vs. deflection (mm) diagram was recorded. The maximal load (N) to break the tablet was determined. Results are presented as mean ± S.D. ($n = 5$).

For some of the formulations, it was impossible to test the strength of the tablets as they showed plastic deformation. To characterise the 'strength' of these tablets a texture analysis was performed (TA-XT2 analyser, Stable Micro Systems, Godalming, UK). The tablet was placed on a support and deformed in a defined, controlled manner by a cone penetration probe over a constant distance of 1 mm using a speed of 0.1 mm/s. A force (N) vs. distance diagram was recorded. The maximal force (N) after 1 mm of penetration was determined. The results are presented as a mean value ± S.D. ($n = 5$).

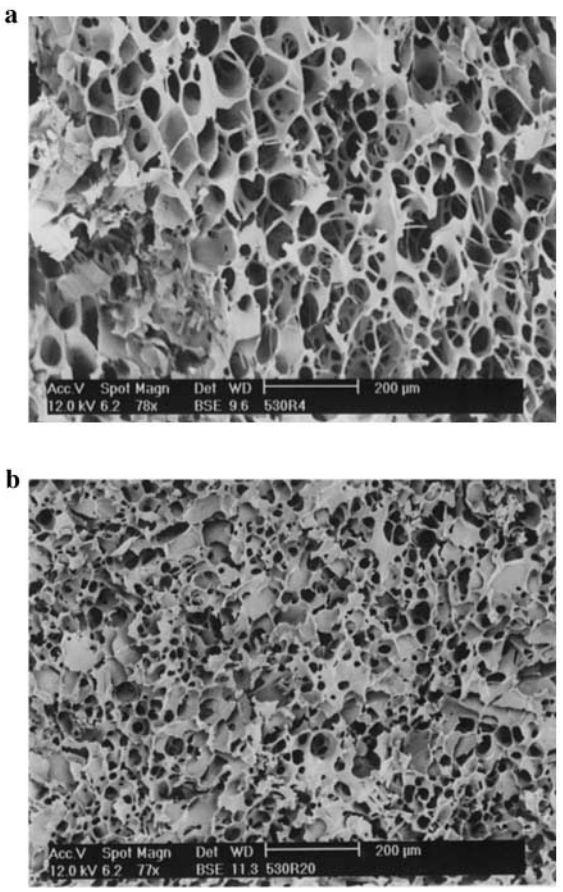

Fig. 1. Scanning electron micrographs of the fracture plane of tablets freeze-dried from a combination of xanthan gum 0.5% (w/v) and maltodextrin DE 38 10% (w/v) (a) and 20% (w/v) (b), respectively.

2.2.5. Disintegration testing

For the determination of the in vivo disintegration time, each subject was given a coded sample and instructed to record the time required for complete disintegration of the tablet when placed on the tongue. All results are presented as a mean value ± S.D. ($n = 5$).

2.2.6. Moisture analysis

The tablets were analysed on their residual moisture content after lyophilisation using Karl Fischer titration (Mettler DL35, Mettler Toledo, Lot, Belgium). The instrument was calibrated using disodium tartrate and water as a standard (Riedel-de-Haen, Seelze, Germany). Each tablet was pulverized, inserted in the titration vessel and analysed after a stirring time of 3 min. Results are presented as a mean value (S.D. ($n = 3$).

2.2.7. Dissolution testing

Dissolution testing was performed on lyophilized tablets containing 50 mg hydrochlorothiazide in 0.1 N HCl (37°C) using the paddle method (USP XXII) at a rotational speed of 100 rpm/min (Vankel dissolution testing station, VanKel International, Hornchurch, UK). Samples of 5 ml were withdrawn at regular time intervals, replaced by fresh medium and spectrofotometrically analysed at 273 nm

(Perkin Elmer Lambda 12 spectrofotometer, PE, Brussels, Belgium) after filtration through a porous metallic filter (pore diameter 2 μm). All dissolution tests were performed in triplicate.

2.2.8. Statistical analysis

Non-parametric statistics were used in order to evaluate the influence of tablet composition on tablet strength and disintegration time as the normal distribution of the data was uncertain. Statistical evaluation on 3 groups of data was done using the non-parametric Kruskal-Wallis test (Siegel and Castellan, 1988) with a significancy level of $P < 0.05$.

A two by two comparison was made on the data by Dunn's post test. Statistical analysis on 2 groups of data was done using the non-parametric Mann-Whitney test with a significance level of $P < 0.01$.

All calculations were done using GraphPad Prism™ ((Version 2.0), San Diego, USA).

3. Results and discussion

Rapidly dissolving tablets can be an interesting oral dosage form for geriatric and pediatric patients. The effectiveness of a sublingual piroxicam fast dissolving dosage form based on lyophilisation has been reported (Auvinet et al., 1995). The choice of the binding agent is an important parameter in the formulation of these products. In a formulation study using lactose as a filler, Vennat et al. (1993) reported that the best results in disintegration time of lyophilised tablets were obtained using cellulose derivatives (e.g. HPMC, MC) as binders. Maltodextrins could be a filler of choice for the production of lyophilised tablets as freeze-drying of a maltodextrin solution results in an amorphous porous network which dissolves in water within seconds. Although a porous pharmaceutical dosage form is produced by freeze-drying, the product is very fragile and difficult to handle. We evaluated gelatins, xanthan gum and hydroxyethylcellulose as binding agents in the formulation of freeze-dried tablets with maltodextrins as filling agent.

3.1. Influence of formulation parameters

Solutions of the maltodextrins DE 38, DE 24 and DE 12 in a 5, 10 and 20% (w/v) concentration were freeze-dried in combination with a constant xanthan gum concentration (0.5% w/v). The disintegration times, strength values and the residual moisture content of the tablets are presented in Table 2. Using a concentration of 5% w/v, the in vivo disintegration time of the DE12 tablets was significantly lower compared to the other tablets made with the maltodextrins ($P < 0.05$). At higher concentrations, however, the in vivo disintegration time of the DE12 tablets was significantly higher ($P < 0.05$). The disintegration time of the tablets was also affected by the maltodextrin concentration. Maltodextrin DE12 concentrations above 5% w/v resulted in in vivo disintegration times above 50 s. The maltodextrins dissolved very fastly, but the xanthan gum swelled upon contact with saliva, forming a jelly structure.

Using a maximum load (N) to evaluate the strength and integrity of the tablets it was difficult to observe a significant relationship between maltodextrin concentration and tablet strength: for all maltodextrins the 20% (w/v) concentration resulted in a significantly higher maximum load (N) value compared to the 5% (w/v) formulations. No significant difference in maximum load (N) could be observed between the 5% and 10% (w/v) and the 10% and 20% (w/v) formulations, respectively. When maximum force (N) was used as a strength parameter a significant influence of the concentration of the maltodextrins, used as a matrix forming agent, on the integrity and strength of the tablets was observed. Higher maltodextrin concentrations resulted in stronger tablets. A significant increase in maximum force was seen with increasing maltodextrin concentrations ($P < 0.01$). No significant difference could be seen between the different DE maltodextrins. The DE value, however, can be an important parameter in lyophilisation process optimisation. The glass transition temperature (Tg') of a frozen solution is an important parameter in lyophilisation. During primary product temperatures above Tg' result in a loss of the microstructure formed during the freezing process

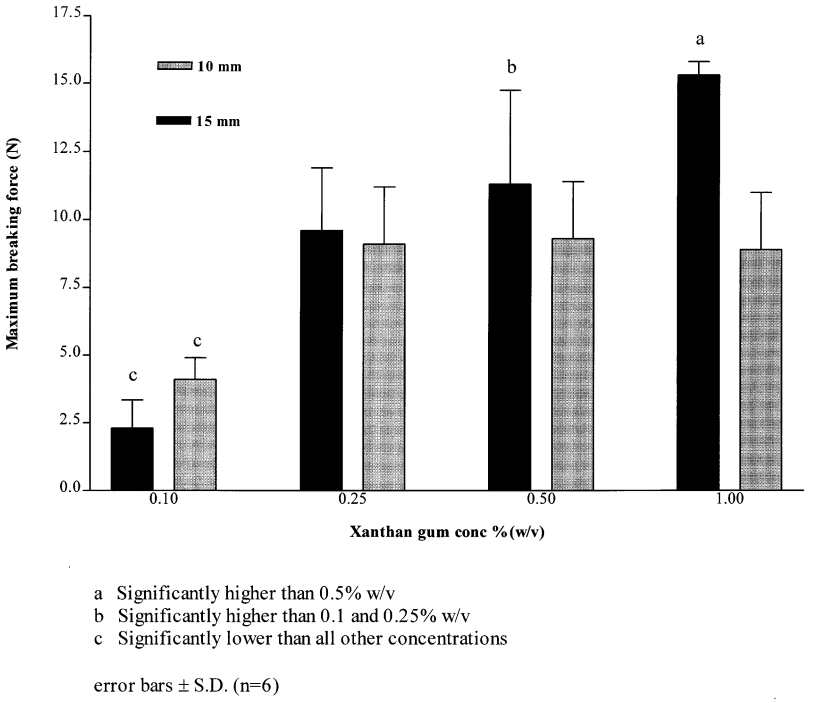

Fig. 2. Strength testing of tablets based on maltodextrin DE38 10% w/v and xanthan gum in different concentrations.

(Her and Nail, 1994). There is a linear relationship between DE value of maltodextrins and the Tg' (Corveleyn and Remon, 1996). With low DE maltodextrins (e.g. DE14, DE22) in freeze drying formulations, higher product temperatures can be used during primary drying because of the high Tg' value. Higher product temperatures result in shorter cycle times, because of an increase in sublimation rate (Pikal, 1991).

Scanning electron micrographs of the fracture plane of tablets containing DE 38 10% and 20% (w/v), in combination with xanthan gum 0.5% (w/v) are shown in Fig. 1a and Fig. 1b, respectively. The maltodextrin concentration had an influence on the pore size of the freeze-dried product. During the freezing step of the process ice crystals are formed. The ability of the ice crystals to grow is smaller when a higher solute concentration is used. The pores in the lyophilized product is what is left of the ice crystals after sublimation (Dawson and Hockley, 1991). A higher maltodextrin concentration in the solutions to be lyophilized, resulted in smaller ice crystals and smaller pore size of the freeze-dried product. The freezing temperature and freezing rate are also critical process parameters, affecting the microstructure of the freeze-dried cake. Fast freezing rates result in small ice crystals and small pore sizes in the microstructure after sublimation of the ice. In this study all formulations, evaluated with S.E.M. were freeze-dried whithin the same lyophilisation cycle. The median pore diameter of the 10 and 20% (w/v) maltodextrin DE 38 formulations, as detemined by mercury porosimetry, was 12.3 ± 0.6 μm for the 10% w/v and 8.8 ± 0.3 μm for the 20% w/v formulations, respectively.

The influence of the xanthan gum concentration (range 0.1–1% w/v) on the characteristics of the tablets was evaluated using DE 38 in a 20% w/v concentration as the matrix forming agent. The strength of the tablets depended on the xanthan gum concentration and the tablet dimensions (Fig. 2). The 0.1% (w/v) formulation resulted in significantly lower strength values compared the other formulations. A tablet strength (15 mm) above 10 N was obtained by using xanthan gum

Table 3
Evaluation of freeze-dried tablets based on the combination of maltodextrins and HEC

Formulation concentration (% w/v)	Disintegration time (s)	Strength	Residual moisture (%)
	in vivo	Maximum force (N)	
HEC 0.25			
Maltodextrin			
DE38			
5	4 ± 1	2.07 ± 0.21	10.17 ± 1.52
10	7 ± 2	5.09 ± 0.53^{b}	8.38 ± 0.58
20	12 ± 2^{b}	12.84 ± 1.19^{c}	6.40 ± 0.65
HEC 0.5			
Maltodextrin			
DE38			
5	10 ± 2^{a}	3.05 ± 0.22^{a}	12.13 ± 1.21
10	13 ± 3^{a}	$5.99 \pm 0.32^{a,b}$	8.19 ± 1.15
20	$17 \pm 4^{a,b}$	14.12 ± 1.52^{b}	6.97 ± 0.84

All results are presented as mean $\pm$ S.D. ($n = 5$).
[a]Significantly higher than 0.25% w/v HEC (Mann Whitney $P < 0.01$).
[b]Significantly higher than 5% w/v maltodextrin ($P < 0.05$)
[c]Significantly higher than 10% w/v maltodextrin ($P < 0.05$).

concentrations above 0.25% w/v. The xanthan gum concentration also had an impact on the viscosity of the solutions prior to freeze-drying. If a drug is suspended in the formulation, the use of a viscosity enhancer is important to avoid sedimentation of the drug particles. The formulations containing 0.5% (w/v) xanthan gum had a viscosity of 466 mPa.s (Haake RV1, 25°C, rotor MV1). However, a xanthan gum concentration above 0.5% (w/v), resulted in longer in vivo disintegration times as the xanthan gum swelled upon contact with the saliva, forming a jelly like structure.

Solutions of the maltodextrin DE 38 in a 5, 10 and 20% (w/v) concentration were also lyophilized in combination with HEC 0.25% and 0.5% (w/v). Results of the disintegration tests, the texture analysis and the residual moisture analysis are shown in Table 3. The disintegration time of these formulations was influenced by the concentration of both the maltodextrin and the HEC. The in vivo disintegration time was significantly higher at 0.5% (w/v) HEC compared to 0.25% (w/v) ($P < 0.01$). Compared to the formulations using xanthan gum as a binder in the same concentration, the disintegration time of the tablets containing HEC was much lower. All tablets freeze-dried from the 0.25% (w/v) HEC formulations disintegrated within 7 s. During strength testing, a plastic deformation of the tablets was seen and it was impossible to measure the strength of these tablets using the tensile strength machine. The tablets strength was then characterised using a texture analysis. The strength value (maximal force) of the tablets depended on the maltodextrin content as a higher maltodextrin concentration resulted in a significant increase in maximal force ($P < 0.01$). At 5% and 10% (w/v) maltodextrin concentration, the maximal force was significantly higher with 0.5% (w/v) HEC as a binding agent compared to 0.25% (w/v) ($P < 0.01$).

Solutions of the maltodextrins DE 38, DE 24 and DE 12 in a 5, 10 and 20% (w/v) concentration were lyophilized in combination with a hydrolised gelatin (Solugel® LB 0.5% w/v). The results of the disintegration tests, the strength tests and residual moisture analysis are shown in Table 4.

The disintegration time of the tablets containing hydrolysed gelatin Solugel® LB as a binder was below 23 s for the in vivo tests. Unlike the xanthan gum formulations, no gel-like structure was formed upon contact with the saliva. A trend could be observed in the of concentration of the matrix forming maltodextrins on the disintegration time of the tablets: increasing the

Table 4
Evaluation of freeze-dried tablets based on the combination of maltodextrins and a hydrolised gelatin Solugel® LB (Bloom value 10–30 g)

Formulation	Disintegration time (s)	Strength (N)		Residual moisture (%)
	in vivo	Maximum load (N)	Maximum force (N)	
Maltodextrin conc (%; w/v)				
DE38				
5	4.0 ± 1.0	4.21 ± 2.11	3.16 ± 0.55	4.11 ± 0.41
10	7.3 ± 2.4	7.78 ± 5.15	5.04 ± 1.10	3.91 ± 0.12
20	12.0 ± 2.0	11.55 ± 3.21^{e}	$14.57 \pm 2.49^{e,f}$	3.41 ± 0.56
DE24				
5	6.0 ± 2.0^{c}	4.17 ± 2.11	4.04 ± 0.68	4.21 ± 1.02
10	14.5 ± 2.5^{b}	10.96 ± 3.12	6.01 ± 1.41	4.01 ± 0.25
20	22.0 ± 5.0^{b}	15.12 ± 6.13^{e}	$15.14 \pm 2.59^{e,f}$	3.89 ± 0.28
DE12				
5	10.0 ± 2.0^{a}	5.11 ± 3.6	3.12 ± 0.49	4.58 ± 0.36
10	8.5 ± 1.5	10.36 ± 6.63	5.77 ± 1.42	4.15 ± 0.21
20	17.0 ± 4.5^{d}	15.15 ± 3.9^{e}	$16.21 \pm 3.43^{e,f}$	3.89 ± 0.55

The gelatin concentration was constant for all formulations (2% w/v).
[a]Significantly higher than DE38 5% w/v ($P<0.05$).
[b]Significantly higher than DE38, same concentration ($P<0.05$).
[c]Significantly lower than 10, 20% w/v DE 24 ($P<0.05$).
[d]Significantly higher than 5%, 10% w/v DE12 ($P<0.05$).
[e]Significantly higher than 5% w/v maltodextrin, same DE ($P<0.05$).
[f]Significantly higher than 10% w/v maltodextrin, same DE ($P<0.05$).

concentration resulted in an increased disintegration time, except for the DE 12 formulations. The strength of the tablets was enhanced by using higher maltodextrin concentrations. The maximum force value for the 20% (w/v) formulation was significantly higher ($P < 0.05$) compared to the 5% and 10% (w/v) formulations, independent on DE value. No significant influence of DE value on the maximal force was observed.

Additionally, tablets were produced using DE 24 in a 5, 10 and 20% (w/v) concentration in combination with different hydrolysed gelatins Solugel® LB (Bloom value 10–30 g), Solugel® P (Bloom value 0 g) and Cryogel 220–400 (Bloom value 220 g) in a concentration of 0.5, 1 and 2% (w/v).

When Solugel® P was used as a binder, the resulting tablets were very friable and fragile, for all concentrations used. Solugel® P is a hydrolysed gelatin having a zero Bloom value. Solugel® LB seemed a good binding agent, but the tablet characteristics were concentration dependent. Higher Solugel® LB concentrations resulted in stronger lyophilized tablets: a significant increase in maximal force (g) was seen ($P < 0.01$). The median pore diameter of the products based on Solugel® LB 2% (w/v), as determined by mercury porosimetry was 19.9 ± 0.6, 15.7 ± 0.7 and 11.7 ± 0.9 μm for the 5, 10 and 20% (w/v) maltodextrin DE 12 formulations, respectively. Scanning electron micrographs of the fracture plain of the tablets are shown in Fig. 3. The influence of maltodextrin concentration on the pore diameter was comparable to the xanthan gum formulations. Using Cryogel, having a Bloom value of 220 g, a gelification of the solutions was seen upon cooling. In the combinations of 2% w/v Cryogel and 10–20% w/v maltodextrin a phase separation of the two polymers in solution was observed. Interactions between gelatins and polysaccharides have been reported by Muyldermans and Vanhoegaerden (1991). These authors showed that cosolution of gelatin and neutral polysaccharides existed when concentra-

tions of both were sufficiently low, with eventually enhanced gel strength properties. At higher concentrations however, thermodynamic incompatibility exists, even phase separation with two distinct layers was described. In the case of maltodextrins the compatibility of gelatins was reported to be lower with a low D.E. maltodextrin than higher D.E. products (Muyldermans and Vanhoegaerden, 1991). In the freeze dried products containing Solugel® LB 3% w/v and Cryogel 1% w/v as binders, a phase separation phenomenon was observed. The resulting tablets were not homogeneous as can be seen from the scanning electron micrographs (Fig. 4).

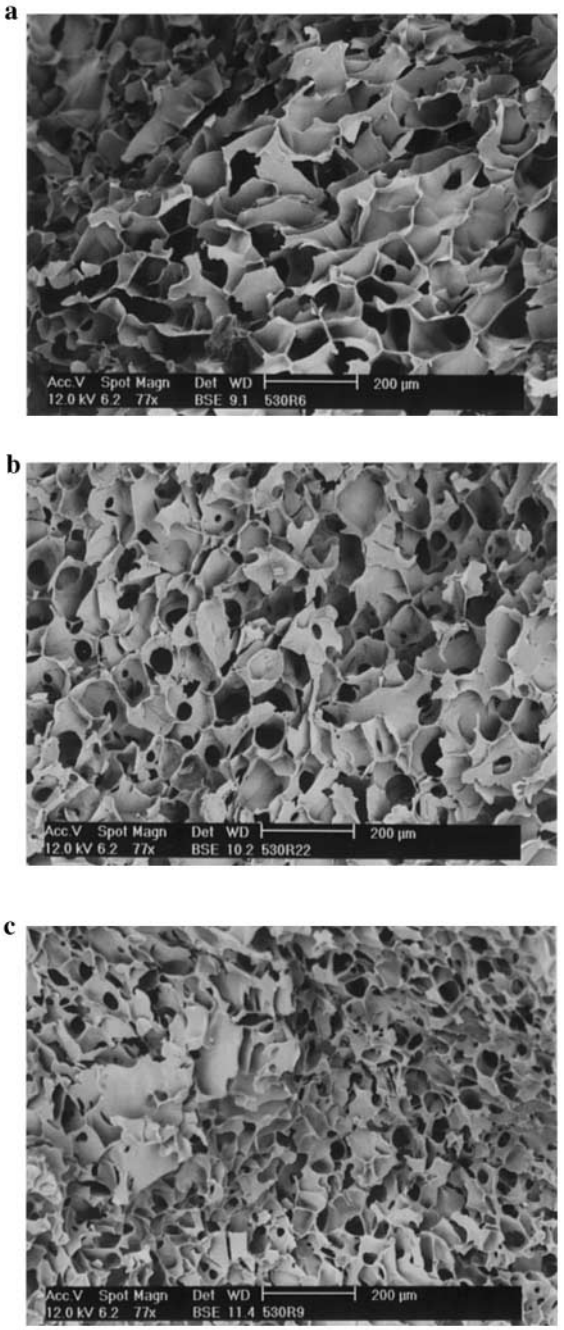

Fig. 3. Scanning electron micrographs of the fracture plane of tablets freeze-dried from a combination of gelatin solugel LB 2% (w/v) and maltodextrin DE 38 5% (w/v) (a), 10% (w/v) (b) and 20% (w/v) (c), respectively.

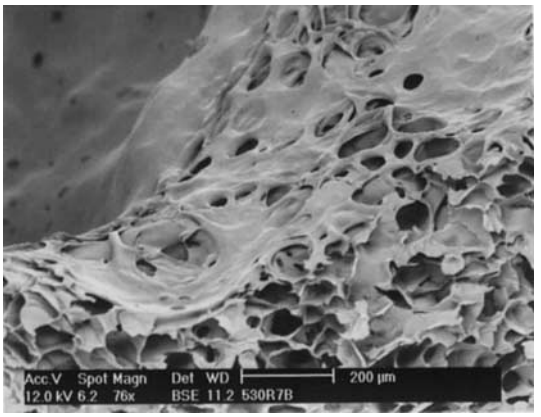

Fig. 4. Scanning electron micrographs of the fracture plane of a tablet freeze-dried from a combination of gelatin Solugel LB 3% (w/v) (Bloom value 10–30) and maltodextrin DE 38 10% (w/v).

Formulations containing 160 mg DE 38 and 4 mg xanthan gum were selected for the manufacturing of tablets containing 50 mg of HCT. The HCT particles were suspended in the tablet matrix.The incorporation of the drug into the formulations led to a decrease in the strength of the tablets. Strength values of 16.61 ± 8.17 N and 4.12 ± 1.41 N were found for the tablets without drug and the tablets containing 50 mg of HCT, respectively. The residual moisture of the tablets was $5.63 \pm 0.51\%$ and $3.75 \pm 0.29\%$ for the tablets without drug and the tablets containing 50 mg of HCT, respectively. The in vitro dissolution profiles of conventional reference tablet and the lyophilized formulations are shown in Fig. 5. The percentage of HCT re-

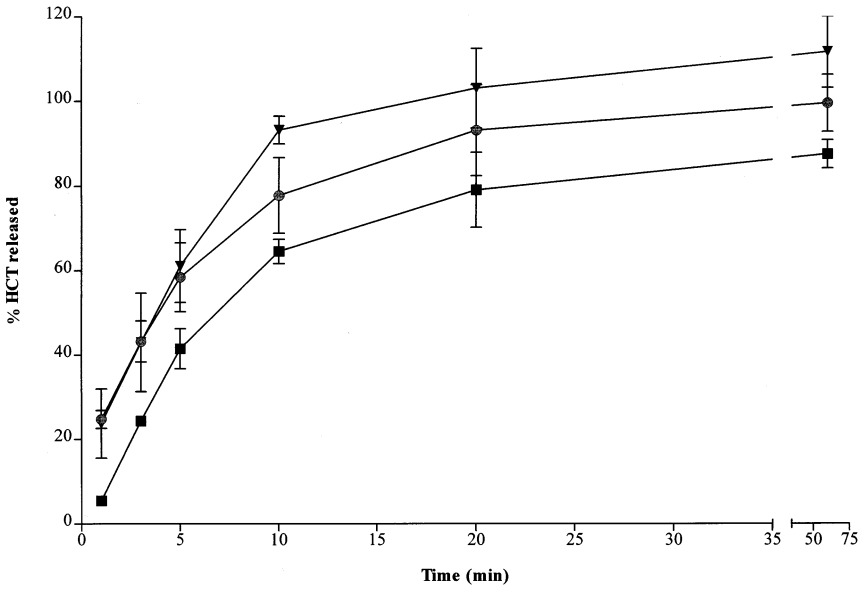

Fig. 5. Dissolution profile of HCT (50 mg) containing formulations: ■ reference tablet; ● lyophilized tablet DE38 160 mg and xanthan gum 4 mg; ▼ lyophilized tablet DE38 160 mg, xanthan gum 4 mg and PEG 6000 8 mg.

leased within 10 min was $64.55 \pm 2.87\%$ and $77.84 \pm 8.94\%$ for the reference tablets and the lyophilized tablet formulation, respectively.

The effect of the addition of 1% PEG 6000 (w/v) to the formulation on the dissolution profile was investigated. Solid dispersions of high molecular weight polyethyleneglycols are reported to increase the in vitro release rate and bioavailability of poorly water soluble drugs (Chiba et al., 1991). Simonelli et al. (1994) reported on the increase of HCT release rate from solid dispersions with PEG 6000. The incorporation of PEG400 into pellet formulations containing HCT, led to an increase of the in vitro release rate of the drug (Vervaet et al., 1994). In our experiments, the addition of PEG 6000 (1% w/v) resulted in an increase of HCT release as 93.3% was released from the lyophilized tablets within 10 min, however, the incorporation of PEG 6000 in the formulation resulted in a decrease in strength of the tablets. Strength values of 4.12 ± 1.41 N and 1.63 ± 0.86N were determined for the tablets containing no PEG and for the tablets containing PEG 6000 (1% w/v), respectively.

3.2. Influence of process parameters

The influence of freezing rate on the characteristics of the tablets was investigated. The evaluated formulations consisted of maltodextrin DE 38 160 mg in combination with xanthan gum 4 mg containing no drug and the same formulation containing 50 mg HCT. Two different freezing rates were evaluated: 0.5 K min^{-1} and 10 K min^{-1}. There was an influence of freezing rate on the strength and residual moisture of the resulting tablets. An increase in freezing rate resulted in a decreased strength (maximum load): for the formulations containing no HCT a strength of 16.6 N (± 5.1) and 3.8 N (± 1.3) was measured using a freezing rate of 0.5 K min^{-1} and 10 K min^{-1}, respectively. For the HCT containing formulations maximum load values of 4.12 N (± 1.41) and 1.44 N (± 0.42) were measured using a freezing speed of 0.5 K min^{-1} and 10 K min^{-1}, respectively. High freezing speed results in a higher degree of supercooling with the formation of small ice crystals (Dawson and Hockley,
Small ice crystals result in a higher surface area and a higher degree of porosity after lyophilisa-

tion, what can be an explanation for a decreased strength of the tablets.

It can be concluded that maltodextrins are a useful matrix forming agent in the formulation of rapidly disintegrating tablets made by lyophilisation. The concentration of the maltodextrin influenced the characteristics of the tablets such as strength and integrity and disintegration time. The choice of the binder is function of the polymer incompatibility and swelling rate.

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