ELSEVIER

International Journal of Pharmaceutics 166 (1998) 65–74

international journal of pharmaceutics

Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs

S. Corveleyn, J.P. Remon *

Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium

Received 20 July 1997; received in revised form 15 December 1997; accepted 21 December 1997

Abstract

The objective was to develop a dry emulsion tablet for the flash delivery of poorly water soluble drugs using a lyophilization technique. The influence of formulation parameters on the characteristics of the lyophilized dry emulsion (LDE) tablets was investigated. Oil-in-water emulsions were made using a medium chain triglyceride as the oil phase and a maltodextrin solution (5–20% w/v) as the water phase. In addition different emulsifier-tablet binder combinations were evaluated. The emulsions were filled into PVC blisters and freeze-dried. The resulting tablets were analyzed for strength, disintegration time, porosity and residual moisture. X-ray diffractions and scanning electron micrographs (SEM) of the fracture plane of the tablets were taken. Dissolution tests were performed on lyophilized tablets containing hydrochlorothiazide (HCT) as a model drug. A significant influence of the maltodextrin type on the tablet disintegration time was seen. Maltodextrin formulations with a high dextrose equivalent (DE) value (DE38) resulted in a faster disintegration time compared to DE12 and DE24 maltodextrin formulations ($p < 0.05$). There was a significant influence of maltodextrin concentration on tablet strength, disintegration time and porosity. Tablet strength increased significantly with increasing maltodextrin concentration ($p < 0.05$). The porosity of the tablets made with DE38 5%, 10% and 20% (w/v) was 92%, 85% and 81%, respectively. SEM pictures showed an increase in pore diameter with a decreasing maltodextrin concentration. No significant influence of Miglyol 812 concentration on tablet strength was observed. A significant influence of methylcellulose concentration, used as emulsifier-tablet binder (Methocel® E15LV), on tablet strength and disintegration time was observed. Dissolution tests on 25 mg HCT containing tablets resulted in a % HCT release of 35.1% and 24.1% for the LDE tablet and conventional tablet, respectively. No significant influence of the oil content in the LDE tablets on the HCT release was observed. It can be concluded that maltodextrins and methylcellulose are useful excipients in the formulation of LDE tablets. The concentration of maltodextrin, the medium chain triglyceride and methylcellulose influenced the tablet characteristics.

Keywords: Dry emulsion tablet; Lyophilized tablet; Maltodextrin; Freeze-drying

* Corresponding author. Tel.: + 32 9 2648056; fax: + 32 9 2228236; e-mail: jeanpaul.remon@rug.ac.be

0378-5173/98/$19.00
PII S0378-5173(98)00024-6

Table 1
Composition of the liquid emulsion formulation and the tablet composition on a dry weight base

Emulsion (% w/w)			Tablet		
			Theoretical composition (mg; w/w)		Weight after lyophilization (mg)
1.	Maltodextrin DE38 (5% w/v)	88	Maltodextrin DE38	35	137 ± 2
	Miglyol 812	10	Miglyol 812	80	
	Methocel® E15LV	2	Methocel® E15LV	16	
2.	Maltodextrin DE38 (10% w/v)	78	Maltodextrin DE38	62	222 ± 5
	Miglyol 812	20	Miglyol 812	160	
	Methocel® E15LV	2	Methocel® E15LV	16	
3.	Maltodextrin DE38 (20% w/v)	68	Maltodextrin DE38	108	369 ± 3
	Miglyol 812	30	Miglyol 812	240	
	Methocel® E15LV	2	Methocel® E15LV	16	
4.	Maltodextrin DE38 (10% w/v)	78	Maltodextrin DE38	62	368 ± 2
	Miglyol 812	20	Miglyol 812	160	
	Methocel® E15LV	2	Methocel® E15LV	16	
	HCT	3.13	HCT	25	

1. Introduction

Paediatric and geriatric patients may have difficulties swallowing or chewing pharmaceutical dosage forms for oral administration. 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.

Solid state emulsions were described by Shively and Myers (1993). Shively reported on the production of solid state emulsions using sucrose and mineral oil (Shively, 1993). Dry emulsions prepared by spray drying an oil-in-water emulsion, containing lactose and maltodextrin in the aqueous phase and griseofulvin as model drug were evaluated as a potential drug delivery system (Pedersen et al., 1995). Freeze drying of an oil-in-water emulsion can be an alternative method for the production of dry emulsions. Bamba et al. (1995) reported that a slow cooling rate and the addition of amorphous cryoprotectants have the best stabilizing effects during lyophilization of oil-in-water emulsions. The characteristics of a dry emulsion containing griseofulvin prepared by lyophilization using mannitol as the solid support was reported by Vyas et al. (1992). Corveleyn and Remon (1997) proved that maltodextrins are a useful matrix forming agent in the formulation of freeze-dried tablets. Lyophilized dry emulsion tablets, using maltodextrins as amorphous cryoprotectant and solid support could be an interesting dosage form for the delivery of poorly soluble drugs. In this study, the influence of different formulation parameters on the characteristics of the lyophilized dry emulsion (LDE) tablets was investigated.

Dissolution studies were performed using hydrochorothiazide as a poorly soluble model drug.

2. Materials and methods

2.1. Materials

The spray-dried maltodextrins (Eridania-Béghin Say-Cerestar, Vilvoorde, Belgium) had different dextrose equivalents (DE) and were obtained by enzymatic hydrolysis of corn starch (C✱PUR01910 (DE = 14), C✱PUR01921 (DE = 22), C✱PUR01934 (DE = 38)), potato starch (C✱PUR01906 (DE = 6)) and waxy maize starch (C✱PUR01908 (DE = 9)). Methylcellulose

Table 2
Influence of maltodextrin DE value and concentration on disintegration time, strength and residual moisture of lyophilised dry emulsion tablets

Formulation		Disintegration time (min)	Strength (N)	Residual moisture (%)
DE6	5% w/v	1.01 ± 0.11	1.01 ± 0.21	1.34 ± 0.02
DE8	5% w/v	1.21 ± 0.15	1.23 ± 0.13	1.30 ± 0.21
DE10	5% w/v	1.50 ± 0.21	1.43 ± 0.25	1.56 ± 0.09
DE12	5% w/v	1.80 ± 0.25	1.41 ± 0.09	1.88 ± 0.02
	10% w/v	5.95 ± 0.47[a]	2.57 ± 0.18	2.39 ± 0.14
	20% w/v	8.15 ± 0.96[a,b]	4.73 ± 0.15[b]	2.46 ± 0.32
DE24	5% w/v	1.0 ± 0.08	1.63 ± 0.04	1.93 ± 0.05
	10% w/v	4.08 ± 0.21[a]	2.70 ± 0.11	1.95 ± 0.15
	20% w/v	7.52 ± 0.38[a,b]	6.46 ± 0.29[b]	2.31 ± 0.18
DE38	5% w/v	0.78 ± 0.12	1.61 ± 0.02	1.85 ± 0.13
	10% w/v	2.41 ± 0.17	3.04 ± 0.10	2.50 ± 0.08
	20% w/v	4.25 ± 0.17[b]	6.58 ± 0.16[b]	1.74 ± 0.18

All tablets contained 160 mg Miglyol 812 as the oil phase and 16 mg Methocel® A15LV as the binder/emulsifier. All results are presented as means ± S.D. ($n = 3$).
[a] Significantly higher than maltodextrin DE38, same concentration ($p < 0.05$).
[b] Significantly higher than 5% w/v ($p < 0.05$).

(Methocel® A15LV, 2% aqueous solution viscosity 15 mPa·s (20°C)), hydroxypropylmethylcellulose (Methocel® E15LV, 2% aqueous solution viscosity 15 mPa·s and Methocel® K100LV, 2% aqueous solution viscosity 100 mPa·s) from Colorcon (Kent, UK) and xanthan gum (Ludeco, Brussels, Belgium) were evaluated as emulsifier-tablet binding agents. A medium chain triglyceride Miglyol 812 (Federa, Belgium) was used as the oil phase. Solutions were made in distilled water. Karl Fischer reagents used were Hydranal Composite 5 and dried methanol (Riedel-de-Haen, Seelze, Germany). Hydrochlorothiazide (HCT) (batch no. 5327 B; Ludeco, Brussels, Belgium) was chosen as model drug having a solubility of 250 mg/l in 0.1 N HCl (25°C). Esidrex® 25 mg (Ciba-Geigy) was chosen as a reference tablet.

2.2. Methods

2.2.1. Preparation of the tablets

Solutions were prepared containing maltodextrins in a concentration ranging from 5 to 20% (w/v) and were used as the water phase of the emulsions in a 60–90% (w/w) ratio. Miglyol 812 was used as the oil phase 10–40% (w/w). All emulsions were prepared using a Silverson mixer (Silverson Machines, Waterside, UK) according to a standardised production protocol described by Kiekens et al. (1997). Tablets were prepared as described previously (Corveleyn and Remon, 1997). PVC blisters with a diameter of 15 mm and a depth of 6 mm were filled with 0.8 g of the emulsion. The blisters were placed on the shelves of the freeze-dryer (Amsco-Finn Aqua GT4, Amsco, Brussels, Belgium). The samples were frozen to -45°C at a rate of 0.5°C 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 -10°C and a condenser temperature of -60°C. Secondary drying was carried out by reducing the pressure to 0.1 mbar and increasing the shelf temperature to 25°C. Secondary drying time was 6 h. Lyophilization was terminated by venting the drying chamber with air. The liquid emulsion formulation and the tablet composition on dry weight base are shown in Table 1.

2.2.2. Scanning electron microscopy

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

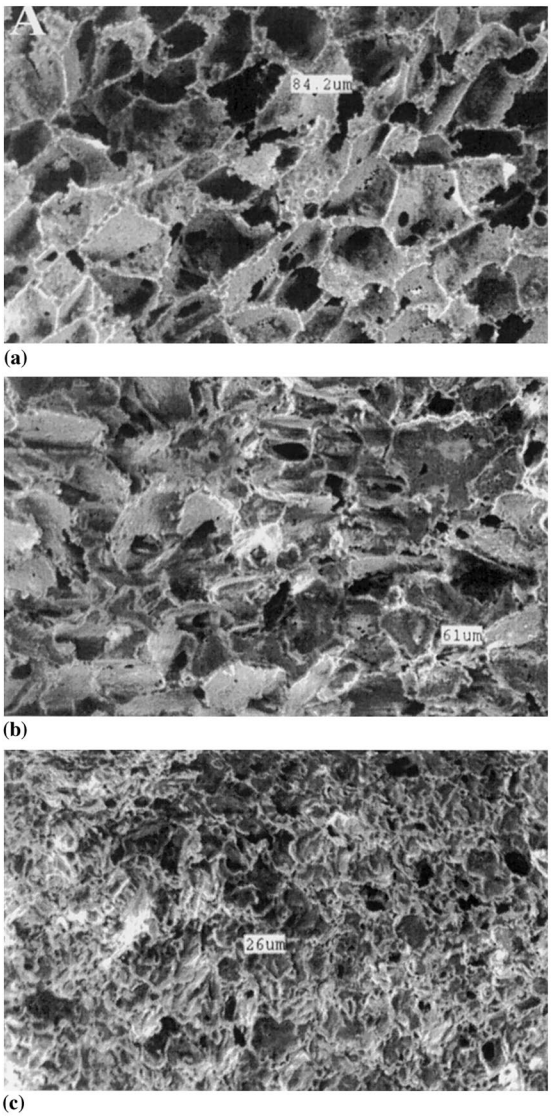

Fig. 1. Scanning electron micrographs of the fracture plane of tablets containing 160 mg Miglyol 812 and 16 mg Methocel® A15LV and different amounts of maltodextrins: (a) 15.5 mg DE38; (b) 31 mg DE38; and (c) 62 mg DE38.

2.2.3. Porosimetric analysis

The pore size and porosity of the tablets was determined using mercury porosimetry (AutoPore III 9420 System, Micromeretics Instruments Corp., Norcross, GA). Results are presented as means $\pm$ S.D. ($n = 3$).

2.2.4. Tablet strength testing

Because of the plastic deformation it was impossible to test the hardness of the tablets on a conventional hardness tester; the strength of the tablets was determined with a texture analyzer (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 (diameter 1.5 mm; height 5 mm) over a constant distance of 1 mm using a speed of 0.1 mm/s. A force (N) versus distance (mm) diagram was recorded. The maximal force (N) after 1 mm of penetration was determined. The results are presented as means $\pm$ S.D. ($n = 3$).

2.2.5. In vivo disintegration testing

For the determination of the in vivo disintegration time (on placebo tablets), each subject was given a coded sample and instructed to place the tablet under the tongue. The time required for complete disintegration of the tablet was recorded. All results are presented as means $\pm$ S.D. ($n = 3$).

2.2.6. Moisture analysis

The tablets were analyzed for their residual moisture content after lyophilization 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 analyzed after a stirring time of 3 min. Results are presented as a means $\pm$ S.D. ($n = 3$).

2.2.7. Droplet size analysis

The lyophilized tablet was reconstituted in 800 μl distilled water and vortexed for 20 s, and the droplet size distribution was determined by visual microscopy (Carl Zeiss, Oberkochen, Germany).

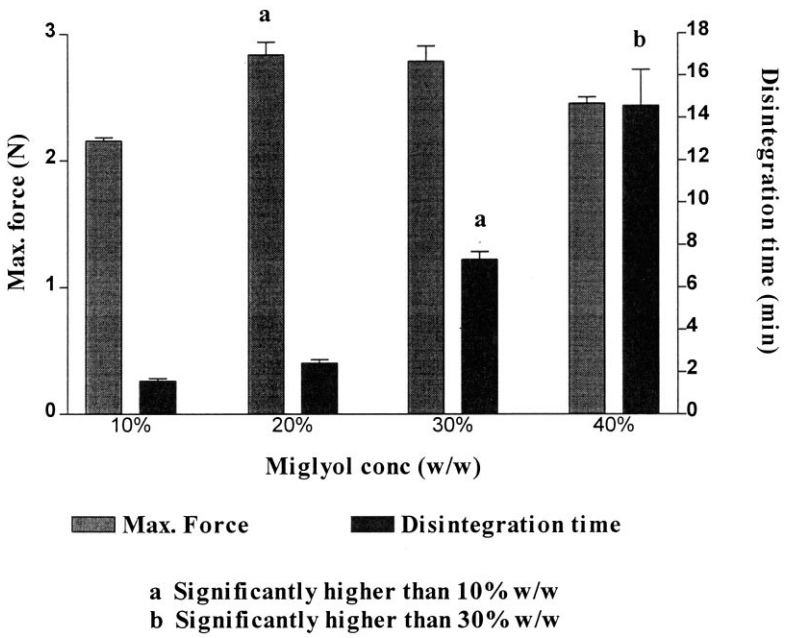

Fig. 2. Influence of Miglyol 812 concentration on tablet strength and disintegration time. Results are presented as means ($n = 3$). Error bars are S.D.

2.2.8. Dissolution testing

Dissolution testing was performed on lyophilized tablets containing 25 mg hydrochlorothiazide (HCT) in distilled water at 37°C using the paddle method (USP XXII) at a rotational speed of 100 rpm (Vankel VK7000 dissolution testing station, VanKel International, Hornchurch, UK). Samples of 5 ml were withdrawn at regular time intervals, replaced by fresh medium by automatic sampling (Vankel VK8000 dissolution sampling station) and spectrophotometrically analyzed at 273 nm (Perkin Elmer Lambda 12 spectrophotometer, PE, Brussels, Belgium). All dissolution tests were performed in triplicate.

2.2.9. Statistical analysis

Statistical evaluation on three groups of data was done using the non-parametric Kruskal–Wallis test (Siegel and Castellan, 1988) with a significance level of $p < 0.05$. A two-by-two comparison was made on the data by Dunn's post test. All calculations were done using GraphPad Prism™, Version 2.0 (San Diego, USA).

3. Results and discussion

It has been reported that emulsified formulations result in an improved absorption of both phenytoin (Chakrabarti and Belpaire, 1978) and griseofulvin (Carrigan and Bates, 1973) compared to non-emulsified lipid formulations. Solid state emulsion refers to the dispersion of an immiscible oil phase within a solid phase (Myers and Shively, 1993). Due to the presence of an oil phase, active ingredients can be dissolved in the oil, eliminating the need for a cosolvent. Different techniques have been described to prepare solid state emulsions including spray drying (Takeuchi et al., 1991a,b), solvent evaporation (Shively, 1993) and freeze-drying (Vyas et al., 1992). The oral bioavailability of vancomycin solid state emulsions (Shively and Thompson, 1995) and vitamin E acetate redispersible dry emulsions (Takeuchi et al., 1991b) has been reported. In this study, the influence of different formulation parameters on the characteristics of tablets prepared by freeze-drying an oil-in-water emulsion was investigated.

Table 3
Influence of binder/emulsifier type and concentration on disintegration time, strength and residual moisture of lyophilised dry emulsion tablets

Binder/emulsifier		Disintegration time (min)	Strength (N)	Residual moisture (%)
Type	Concentration			
Methocel® E15LV	2% w/v	0.92 ± 0.09	2.85 ± 0.54	2.15 ± 0.06
Methocel® A15LV	2% w/v	1.21 ± 0.05	3.05 ± 0.21	1.65 ± 0.08
Methocel® K100LV	2% w/v	1.26 ± 0.06	2.74 ± 0.12	1.99 ± 0.01
Xanthan gum	0.25% w/v	1.11 ± 0.12	0.62 ± 0.01	2.52 ± 0.14
	0.5% w/v	1.71 ± 0.03[a]	0.82 ± 0.02[a]	2.41 ± 0.01
	1% w/v	2.46 ± 0.17[b]	0.78 ± 0.01	2.85 ± 0.34

All tablets contained 62 mg maltodextrin DE38 and 160 mg Miglyol 812. The results are presented as means $\pm$ S.D. ($n = 3$).
[a] Significantly higher than 0.25% w/v ($p < 0.05$).
[b] Significantly higher than 0.5% w/v ($p < 0.05$).

The influence of the maltodextrin type and concentration on the disintegration time, strength and residual moisture is shown in Table 2. No significant influence of the maltodextrin type (corn starch, potato starch or waxy maize starch) and DE value at a 5% w/v concentration on the disintegration time and tablet strength was observed.

At higher maltodextrin concentrations (10% and 20% w/v), the disintegration time of the DE38 corn starch maltodextrin formulations was significantly lower than the DE12 and DE24 corn starch maltodextrins ($p < 0.05$). There was a significant influence of maltodextrin content on the disintegration time and tablet strength ($p < 0.05$). The tablet strength increased linearly with increasing maltodextrin concentration. The maltodextrin concentration also had an effect on the porosity of the tablets. The tablet porosity decreased with increasing DE38 concentration from 5 to 20% w/v and ranged from $92.9 \pm 3.5\%$ to $80.9 \pm 3.2\%$. Scanning electron micrographs of the fracture plane of the DE38 5%, 10% and 20% w/v tablets (Fig. 1) showed clearly a decrease in pore diameter with increasing maltodextrin concentrations. This is in accordance with previously published results on the formulation of freeze-dried tablets (Corveleyn and Remon, 1997). Since higher maltodextrin concentrations in the solution to be freeze-dried, resulted in smaller ice crystals, smaller pore sizes were observed in the freeze-dried tablet. No significant effect of maltodextrin type, DE value or concentration on the tablet residual moisture was observed.

The influence of the oil (medium chain triglyceride) concentration on tablet strength and disintegration time is shown in Fig. 2. An increase in Miglyol 812 content resulted in a significant increase in disintegration time ($p < 0.05$) while the tablet strength was not influenced. The residual moisture of the tablets decreased with increasing Miglyol 812 concentration probably due to the lower initial water content of the emulsion. A decrease in median pore diameter with increasing Miglyol 812 concentration was determined by porosimetric analysis. A mean median pore diameter of 29.4 ± 3.1 μm, 15.8 ± 0.9 μm, 10.5 ± 4.4 μm and 6.3 ± 1.1 μm was measured for the 10% w/w, 20% w/w, 30% w/w and 40% w/w Miglyol 812 formulations, respectively. This trend was confirmed by the scanning electron microscopy pictures. The excipients used as emulsifiers in the preparation of the emulsion, should also have good tablet binding properties. Methylcellulose and hydroxypropylmethylcellulose have been reported as emulsifying agents in the preparation of oil-in-water emulsions (Kiekens et al., 1997). These emulsifiers could also act as a tablet binder in the production of lyophilized dry emulsion tablets.

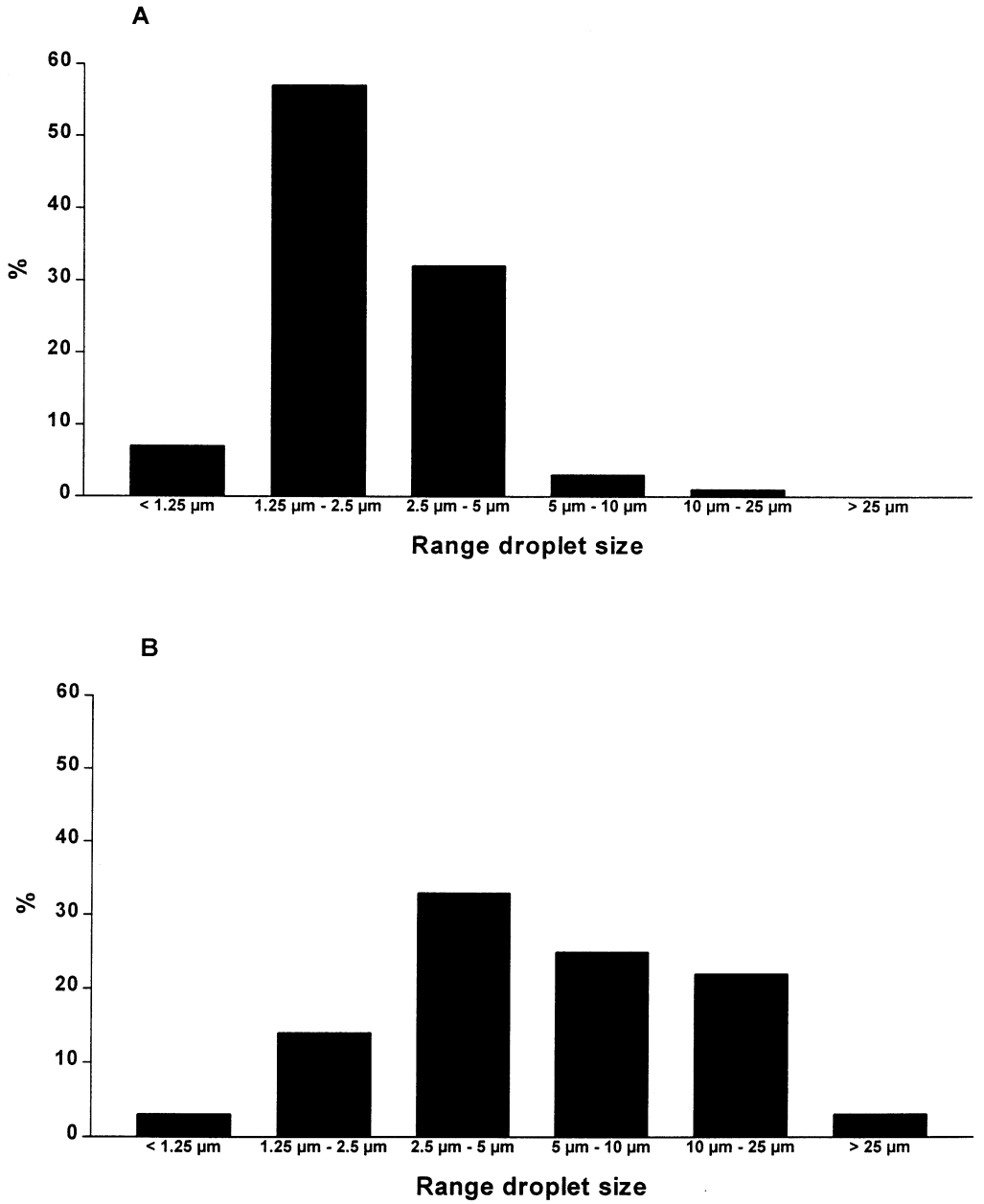

Fig. 3. Droplet size distribution ($n = 100$) of (A) an emulsion before freeze-drying and (B) a reconstituted lyophilized tablet. The emulsion composition is 10% w/v maltodextrin DE38 solution and Miglyol 812 in a 80:20 (w/w) ratio and 2% w/v Methocel® A15LV.

Different types of Methocel® were evaluated as potential emulsifier-binders. The Methocel® concentration had a significant influence on the tablet strength and disintegration time. The effect of emulsifier/binder type and concentration on lyophilized tablet characteristics is shown in Table 3. The choice between methylcellulose and hydroxypropylmethylcellulose had no significant ef-

fect on tablet disintegration time, strength and residual moisture but determined only the viscosity of the emulsion prior to freeze-drying: a viscosity of 112 mPa·s, 121 mPa·s and 292 mPa·s (Haake RV1, 25°C, rotor MV1) was measured for the emulsions containing 2% w/v Methocel® E15LV, 2% w/v Methocel® A15LV and 2% w/v Methocel® K100LV, respectively. The strength of the tablets containing xanthan gum as a binder was significantly lower compared to the Methocel® containing tablets. Xanthan gum was tested in the concentration range 0.25–1% w/v because higher concentrations resulted in an unacceptably high emulsion viscosity. Xanthan gum concentrations above 0.5% w/v resulted in long tablet disintegration times, because of surface swelling upon contact with the saliva (Corveleyn and Remon, 1997). Besides, a higher xanthan gum concentration induced a significantly higher tablet disintegration time ($p < 0.05$).

Since a real dry emulsion should be able to reconstruct the original emulsion system on dispersing in an aqueous medium, a droplet size distribution analysis was performed before freeze-drying and after tablet reconstitution. The droplet size distribution of the original emulsion before lyophilization, containing 10% w/v maltodextrin DE38 solution as the water phase and Miglyol 812 as the oil phase in a 80:20 (w/w) ratio, with Methocel® A15LV (2% w/v) as the emulsifier, and of the reconstituted tablet emulsion are presented in Fig. 3. The mean droplet diameter was 2.1 μm (range 0.5–20.0 μm) and 5.4 μm (range 1.0–50.0 μm) for the original emulsion and the reconstituted tablet, respectively.

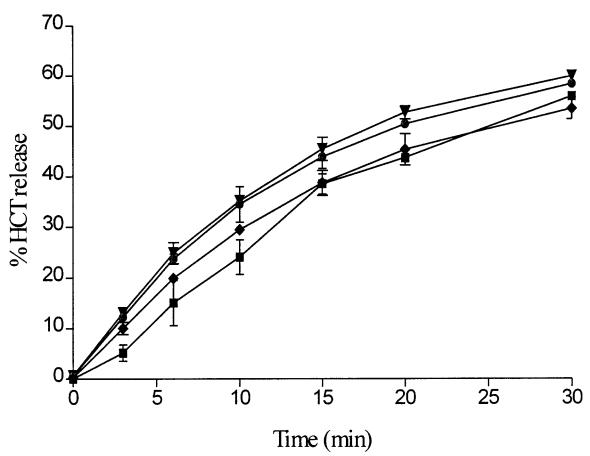

Fig. 4. Dissolution profile of 25 mg HCT containing tablets. All lyophilized tablets contained 62 mg DE38 and 16 mg Methocel® A15LV. ■ reference tablet, ● lyophilized tablet with 80 mg Miglyol 812, ▼ lyophilized tablet with 160 mg Miglyol 812, and ◆ lyophilized tablet with 240 mg Miglyol 812.

Takeuchi et al. (Takeuchi et al., 1991a,b) reported on the formulation and bioavailability of a redispersible dry emulsion as a novel oral dosage form for vitamin E acetate (VEA). The in vitro drug release of this spray-dried system depended on the type of additive: the % VEA released after 60 min was 1.6% and 69.4% for the formulations containing lecithin and Tween 80, respectively (Takeuchi et al., 1991a). Shively and Thompson (1995) showed a 30% bioavailability of vancomycin after oral administration of a solid state emulsion in rats. In our study in vitro dissolution tests were performed in distilled water on tablets containing 25 mg hydrochlorothiazide, 62 mg maltodextrin DE38, 80–240 mg Miglyol 812 and 16 mg Methocel® A15LV. The dissolution profiles are shown in Fig. 4. A 35.1 ± 2.3% release of HCT was seen after 10 min for the 80 mg Miglyol 812 LDE tablet. A conventional tablet showed 24.1 ± 1.2% HCT release after 10 min. It was previously reported that the incorporation of suspended material into a freeze-dried tablet resulted in the appearance of crystals into the matrix, detected by SEM and in a decrease in tablet strength (Corveleyn and Remon, 1997). Although no crystals were observed on the scanning electron micrographs of the LDE tablets containing HCT, X-ray diffraction of the tablets revealed a crystalline HCT fraction. The incorporation of HCT in the tablets led to a decrease in tablet strength: a maximal force of 3.6 ± 0.6 N and 1.7 ± 0.5 N was measured for the placebo and HCT containing tablets, respectively and indicated that the drug was suspended into the tablet matrix. The HCT was not completely dissolved in the oil phase prior to freeze-drying, resulting in partially suspended HCT in the tablet. The oil content of the tablets was increased to evaluate the effect on HCT dissolution. No significant influence of oil content in the tablets on HCT

release was detected: $34.6 \pm 2.1\%$, $35.1 \pm 1.3\%$ and $38.8 \pm 1.6\%$ HCT was released after 10 min for the 80, 160 and 240 mg Miglyol 812 containing tablets, respectively. No significant difference in in vitro HCT release was seen between the conventional tablet and the LDE tablet formulations.

Freeze-dried emulsion tablets might offer advantages in the formulation of drugs for which the bioavailability is enhanced by fat co-administration, for which it is known that emulsion formulations reduce variability in bioavailability, and for drugs with a low water solubility. Besides it is a viable alternative to the use of liquid emulsions so avoiding stability and compliance problems. Although no significant difference in in vitro drug release was observed between the conventional and the LDE tablets, in vivo data would be useful since the co-administration of lipids can reduce the limitations of slow and incomplete dissolution of poorly water soluble drugs and facilitate the formation of solubilised phases from which absorption might occur (Humberstone and Charman, 1997). Especially in the case of lipid based oral delivery systems, digestion of the oily components of the formulation can be advantageous in that the drug may be solubilised within mixed micelles of bile components and products of triglyceride lipolysis (Macgregor et al., 1997). An in vivo bioavailability study to evaluate the possible advantages of lyophilized dry emulsion tablets, on the bioavailability of poorly soluble drugs is ongoing.

It can be concluded that maltodextrins are a useful excipient in the formulation of lyophilized dry emulsion tablets. Methocel® can be used as a emulsifier-tablet binding agent. The concentrations of maltodextrin, Miglyol 812 and Methocel® influenced the tablet characteristics such as strength, disintegration time and porosity.

Acknowledgements

The authors wish to thank Eridania-Béghin Say-Cerestar (Vilvoorde, Belgium) for the generous supply of the maltodextrins and for the use of the TAXT2 texture analyzer. Methocel® was kindly provided by Colorcon (Kent, UK). Prof. Wettinck (Lab. Non-Ferrometallurgie, University of Gent, Belgium) is kindly acknowledged for the use of the scanning electron microscope.

References

Bamba, J., Cavé, G., Bensouda, Y., Tchoreloff, P., Puisieux, F., Couarraze, G., 1995. Cryoprotection of emulsions in freeze-drying: freezing process analysis. Drug Dev. Ind. Pharm. 21, 1749–1760.

Carrigan, P.J., Bates, T.R., 1973. Biopharmaceutics of drugs administered in lipid-containing dosage forms. I: GI absorption of griseofulvin from oil-in-water emulsion in the rat. J. Pharm. Sci. 62, 1476–1479.

Chakrabarti, S., Belpaire, F.M., 1978. Bioavailability of phenytoin in lipid containing dosage forms in rats. J. Pharm. Pharmacol. 30, 330–331.

Corveleyn, S., Remon, J.P., 1997. Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. Int. J. Pharm. 152, 215–225.

Humberstone, A.J., Charman, W.N., 1997. Lipid-based vehicles for the oral delivery of poorly water soluble drugs. Adv. Drug Del. Rev. 25, 103–128.

Kiekens, F., Vermeire, A., Samyn, N., Demeester, J., Remon, J.P., 1997. Optimisation of electrical conductance measurements for the quantification and prediction of phase separation in o/w-emulsions, containing hydroxypropylmethylcelluloses as emulsifying agents. Int. J. Pharm. 146, 239–245.

Macgregor, K.J., Embleton, J.K., Lacy, J.E., Perry, E.A., Solomon, L.J., Seager, H., Pouton, C.W., 1997. Influence of lipolysis on drug absorption from the gastro-intestinal tract. Adv. Drug Del. Rev. 25, 33–46.

Myers, S.L., Shively, M.L., 1993. Solid-state emulsions: the effect of maltodextrin on microcrystalline aging. Pharm. Res. 10 (9), 1389–1391.

Pedersen, G.P., Faldt, P., Bergenstahl, B., Kristensen, H.G., 1995. Dry emulsions as a potential drug delivery system. In: Proceedings of the 1st World Meeting APGI/APV, Budapest, pp. 641–642.

Shively, M.L., 1993. Characterizaton of oil-in-water emulsions prepared from solid-state emulsions: effect of matrix and oil phase. Pharm. Res. 10, 1153–1156.

Shively, M.L., Myers, S., 1993. Solid-state emulsions: the effects of process and storage conditions. Pharm. Res. 10, 1071–1075.

Shively, M.L., Thompson, D.C., 1995. Oral bioavailability of vancomycin solid state emulsions. Int. J. Pharm. 117, 119–122.

Siegel, S., Castellan Jr., N.J., 1988. Nonparametric Statistics. McGraw-Hill International Editions, Singapore.

Takeuchi, H., Sasaki, H., Niwa, T., Hino, T., Kawashima, Y., Uesugi, K., Kayano, M., Miyake, Y., 1991a. Preparation

of powdered redispersible vitamin E acetate emulsion by spray drying technique. Chem. Pharm. Bull. 39, 1528–1531.

Takeuchi, H., Sasaki, H., Niwa, T., Hino, T., Kawashima, Y., Uesugi, K., Ozawa, H., 1991b. Redispersible dry emulsion system as a novel oral dosage form of oily drugs: in vivo studies in beagle dogs. Chem. Pharm. Bull. 39, 3362–3364

Vyas, S.P., Jian, C.P., Kaushik, A., Dixit, V.K., 1992. Preparation and characterization of griseofulvin dry emulsion. Pharmazie 47, 463–464.