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Preparation of redispersible dry emulsions by spray drying

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Abstract

Development of stable dry emulsions being able to reform the original o/w-emulsion by reconstitution in water is presented. Dry emulsions were prepared by spray drying liquid o/w-emulsions in a laboratory spray dryer. Three hydroxypropylmethylcellulose (HPMC) types were applied as solid carrier and emulsifier. The lipid phase was fractionated coconut oil. The ratio of solid carrier to lipid phase influenced the reconstitution properties. It was possible to prepare redispersible dry emulsions of a lipid content up to 40% dry powder mass. The different HPMC types had no noticeable effect on the reconstitution properties, but too viscous liquid o/w-emulsions were difficult to atomise. The type of rotary atomizer, or the rate of rotation did not affect the technical properties of the dry emulsions containing 40% lipid. It was concluded that low viscosity HPMC was a useful solid carrier. The dry emulsions remained physically stable for at least 6 months. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Spray drying; Dry emulsion; Lipid; Hydroxypropylmethylcellulose (HPMC); Microencapsulation; Redispersibility

1. Introduction

Dry emulsions present a potential oral drug delivery system for lipophilic and low soluble drug substances and for drug substances needing protection against light (Takeuchi et al., 1992b) or oxidation (Heinzelmann and Franke, 1999) because they are powdery, lipid-based formulations from which an o/w-emulsion can easily be reconstituted in vivo (Takeuchi et al., 1991b; Porter et al., 1996; Corveleyn and Remon, 1998b) or when exposed to an aqueous solution (Richter and Steiger-Trippi, 1961; Lladser et al., 1968; Nakamoto et al., 1975; Macheras and Reppas, 1986; Takeuchi et al., 1991a, 1992a,b; Myers and Shively, 1992; Vyas et al., 1992; Shively, 1993a,b; Molina and Cadorniga, 1995; Shively and Thompson, 1995; Porter et al., 1996; Corveleyn and Remon, 1998a; Pedersen et al., 1998).

Dry emulsions have been prepared by drying liquid o/w-emulsions containing a soluble or an insoluble solid carrier in an aqueous medium. By drying, the aqueous phase is removed causing the solid carrier to encapsulate the dispersed lipid phase. The aqueous phase has been removed by spray drying (Richter and Steiger-Trippi, 1961; Nakamoto et al., 1975; Takeuchi et al., 1991a,

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1992a,b; Fäldt and Bergenståhl, 1995, 1996a,b,c; Pedersen et al., 1998), by lyophilisation (Lladser et al., 1968; Macheras and Reppas, 1986; Vyas et al., 1992; Molina and Cadorniga, 1995; Corveleyn and Remon, 1998a,b, 1999; Heinzelmann and Franke, 1999) and by rotary evaporation (Myers and Shively, 1992, 1993; Shively, 1993a,b; Shively and Myers, 1993; Shively and Dec, 1994; Shively and Thompson, 1995; Porter et al., 1996).

Dry emulsions have been prepared by application of a soluble carrier such as gelatine (Nakamoto et al., 1975), glycine (Lladser et al., 1968), lactose (Lladser et al., 1968; Shively, 1993a; Fäldt and Bergenståhl, 1995, 1996a,b,c; Pedersen et al., 1998; Heinzelmann and Franke, 1999), maltodextrin (Myers and Shively, 1993; Shively, 1993a; Corveleyn and Remon, 1998a,b, 1999; Pedersen et al., 1998; Heinzelmann and Franke, 1999), mannitol (Lladser et al., 1968; Vyas et al., 1992; Shively, 1993a; Molina and Cadorniga, 1995), povidone (Lladser et al., 1968; Vyas et al., 1992; Shively, 1993a,b), sucrose (Lladser et al., 1968; Myers and Shively, 1992, 1993; Vyas et al., 1992; Shively, 1993a; Shively and Myers, 1993; Shively and Dec, 1994; Shively and Thompson, 1995; Porter et al., 1996) and an insoluble carrier such as colloidal silica (Lladser et al., 1968; Takeuchi et al., 1991a,b, 1992a,b; Vyas et al., 1992).

By processes such as spray drying, lyophilisation and rotary evaporation, the solid carrier may undergo partial or complete transformation into an amorphous state. Physical stability problems arise, because the amorphous carrier exhibits a strong tendency to crystallise, in particular at elevated temperatures and relative humidities. Stability of dry emulsions containing lactose (Lladser et al., 1968; Fäldt and Bergenståhl, 1995, 1996a,b,c; Pedersen et al., 1998; Heinzelmann and Franke, 1999), maltodextrin (Myers and Shively, 1993; Pedersen et al., 1998; Corveleyn and Remon, 1999; Heinzelmann and Franke, 1999), mannitol (Lladser et al., 1968; Molina and Cadorniga, 1995) and sucrose (Lladser et al., 1968; Myers and Shively, 1993; Shively and Myers, 1993) were investigated. For amorphous lactose (Fäldt and Bergenståhl, 1995, 1996a,b,c; Pedersen et al., 1998) and amorphous sucrose (Myers and Shively, 1993; Shively and Myers, 1993) crystallisation was seen. Crystallisation of amorphous lactose was not inhibited by adding maltodextrin (Pedersen et al., 1998), whereas inhibition of the crystallisation of amorphous sucrose was observed when applying concentrations of maltodextrin from 50% and above (Myers and Shively, 1993).

In the present study, dry emulsions containing water-soluble polymers as solid carrier were prepared by spray drying. Water-soluble polymers were applied to avoid unstable amorphous disaccharides. Preliminary studies were conducted applying three water-soluble polymers: hydroxypropylmethylcellulose (HPMC), methylcellulose and povidone. These studies confirmed that dry emulsions composed of HPMC were the most promising. HPMC facilitated the emulsification of liquid o/w-emulsions due to its ability to reduce the surface tension. By increasing the content of HPMC in liquid o/w-emulsions a reduced droplet size distribution was obtained (Kiekens et al., 1997). Problems by spray drying liquid o/w-emulsions with a high concentration of HPMC may arise, such as a blocked atomizer, because aqueous solutions of HPMC exhibit thermoreversible gelation. HPMC types gel on heating and re-dissolve on cooling (Sarkar, 1995; Ford, 1999) and at the thermal gelation temperature, the viscosity of the solution increases (Ford, 1999). To dry highly concentrated HPMC liquid o/w-emulsions optimisation of the spray drying process can be obtained by reducing the temperature at the atomizer by water-cooling. Fractionated coconut oil was applied as the lipid phase. Fractionated coconut oil is liquid at room temperature and is made up of short or middle chain triglycerides containing only saturated fatty acids making it stable to oxidation.

The objective of the present study was to develop stable dry emulsions, which reconstitute the original o/w-emulsion in water. The study was performed by spray drying various liquid o/w-emulsions containing fractionated coconut oil dispersed in aqueous solutions of HPMC. The spray drying process, the reconstitution properties and the stability of the dry emulsions were investigated.

2. Materials and methods

2.1. Materials

HPMC (Pharmacoat 603, Pharmacoat 645 and Pharmacoat 606) were obtained from Shin-Etsu, Japan. The viscosity of the three polymers is 3.0, 4.4 and 6.1 mPas (2% w/v solution) at 20°C, respectively. Fractionated coconut oil (Miglyol 812 N) was supplied by Condea, Germany.

2.2. Preparation of dry emulsions

A total of 500 ml of liquid o/w-emulsions were prepared with 20% dry powder mass. The aqueous solution containing dissolved HPMC and the fractionated coconut oil were homogenised in a high speed colloid mill, Ultra-Turrax® T25 basic (IKA Labortechnik, Germany) for 3 min at 24 000 rpm.

The liquid o/w-emulsions were spray dried in a laboratory spray dryer, Mobile Minor (Niro Atomizer, Denmark). The drying chamber diameter is 180 mm, and the cylindrical height is 600 mm and conical-based. The dryer operates co-currently, has a standard rotary atomizer and a flow of drying air at approximately 135 kg/h.

2.3. Reconstitution of liquid emulsions

A total of 1.0 g of dry emulsion was suspended in 4.0 ml of distilled water in a 17 ml container. After 1 h of rotation at approximately 20 rpm (comfort Heto Mastermix rotator), samples were withdrawn for further characterisation.

2.4. Storage of dry emulsions

The dry emulsions were stored in well-closed containers protected from light at ambient temperature and relative humidity. Samples were taken out to be stored for 6 months at ambient temperature and 40°C in 75% relative humidity in a humidity chamber created by a saturated NaCl solution.

2.5. Study design

A 3-step study plan was set up. The first step was to develop dry emulsions with different lipid contents, which reconstitute the original o/w-emulsion when exposed to water. The lipid contents varied from 30 to 80% of the dry powder mass applying Pharmacoat 603 as the solid carrier. The effects of different HPMC types on the reconstitution properties of the dry emulsions were investigated. Dry emulsions with a lipid content of 50% were prepared with three HPMC types, Pharmacoat 603, 645 and 606. In the spray drying process a vaned wheel atomizer of 35 000 rpm was applied. The inlet air temperature was 100°C and the outlet air temperature was held at 75°C. Water-cooling at the atomizer was applied for spray drying the liquid o/w-emulsions containing Pharmacoat 606.

Subsequently the effects of two spray drying parameters on the technical properties of the dry emulsions containing 40% lipid and Pharmacoat 603 were studied. A complete 2^2 factorial experiment with two replications was performed by varying the type of atomizer, vaned wheel and rotary cup (Masters, 1991), and the rotation rate, 25 000 and 35 000 rpm. In the spray drying process, water-cooling at the atomizer was applied. The inlet air temperature was 120°C and the outlet air temperature was held at 75°C.

Finally the physical stability of the dry emulsions upon ageing was tested. The dry emulsions containing 40% lipid and Pharmacoat 603 were selected.

2.6. Characterisation of liquid emulsions

The droplet size distribution of the o/w-emulsions before spray drying and after reconstitution was determined by laser diffraction, Mastersizer S (Malvern Instruments, UK). A Reverse Fourier optic lens with a 300 focal length was used, covering the size interval 0.05–880 μm. The refractive index of lipid was 1.4500, the absorption value was 0.1 and the refractive index of water was 1.3300. The droplet size distribution was determined on the basis of the volume distribution. The volume weighted median diameter, $d(v, 0.5)$,

was applied to characterise the droplet size. The width of the droplet size distribution was expressed by the SPAN value:

$$\text{SPAN} = \frac{(d(v, 0.9) - d(v, 0.1))}{d(v, 0.5)}$$

2.7. Characterisation of dry emulsions

2.7.1. Density

The density of the dry emulsions was determined by helium pycnometry, AccuPyc 1330 pycnometer (Micrometritics, UK). An equilibration rate of 0.7 kPag/min was chosen, and for one determination each sample was measured seven times. A Pascal 140 equipped with a dilatometer type CD3P (Fisons Instruments, Italy) was applied to determine the density of the dry emulsions by mercury porosimetry.

2.7.2. Moisture content

The moisture content of the dry emulsions was determined by ThermoGravimetric Analysis (TGA) applying a TGA 7 equipped with an instrument controller TAC 7/PC (Perkin Elmer, Denmark). 15.00–20.00 mg samples were placed in the sample pan and the effluent gas was dry nitrogen. The scanning rate was 10°C/min in the scan range 50–200°C. The moisture content was determined as the weight loss between 50 and 120°C. The instrument was calibrated towards Alumel and Nickel in addition to a furnace and weight calibration.

2.7.3. Surface characterisation

The outer macroscopic structure of the dry emulsions was examined by scanning electron microscopy (SEM), JMS-5200 scanning electron microscope (Jeol, Japan). Prior to microscopy, samples were coated with gold/palladium by sputtering for 300 seconds in a BioRad, E5200 Auto Sputter Coater. The samples were scanned at a voltage of 15 kV.

2.8. Data analysis

Data obtained from the complete 2^2 factorial experiment with two replications were evaluated by ANOVA (analysis of variance). Statgraphics Version 7.0 (Manugistics, USA) was used for the statistical calculations.

3. Results

3.1. Dry emulsions

3.1.1. Dry emulsions with a varied lipid content

Table 1 shows that the droplet size distribution of the liquid o/w-emulsions before spray drying and after reconstitution increased with increasing lipid content. Dry emulsions having a lipid content below 50% reformed the original emulsion. During reconstitution, bidisperse systems were obtained for dry emulsions containing more than 50% lipid giving rise to larger $d(v, 0.5)$ and SPAN-values in the reconstituted o/w-emulsions. Contrary to the droplet size, the particle size of the

Table 1
Droplet size distribution of the liquid o/w-emulsions before spray drying and after reconstitution[a]

Formulation containing	Liquid emulsion		Reconstituted emulsion	
	$d(v, 0.5)$ (μm)	SPAN	$d(v, 0.5)$ (μm)	SPAN
30% Lipid	0.82 (0.03)	0.97 (0.06)	0.79 (0.01)	1.10 (0.04)
40% Lipid	0.91 (0.02)	0.95 (0.06)	1.08 (0.00)	1.29 (0.03)
50% Lipid	1.17 (0.02)	0.96 (0.00)	1.53 (0.04)	1.59 (0.10)
60% Lipid	1.60 (0.06)	0.97 (0.05)	2.18 (0.01)	1.83 (0.03)
70% Lipid	2.28 (0.08)	1.08 (0.03)	3.13 (0.07)	3.49 (0.28)
80% Lipid	3.15 (0.07)	1.93 (0.06)	7.73 (0.36)	3.88 (0.23)

[a] The values are the mean value of two determinations and values in brackets are the difference between the two determinations.

Table 2
Droplet size distribution of the liquid o/w-emulsions before spray drying and after reconstitution[a]

Formulation containing	Liquid emulsion		Reconstituted emulsion	
	$d(v, 0.5)$ (μm)	SPAN	$d(v, 0.5)$ (μm)	SPAN
Pharmacoat 603	1.17 (0.02)	0.96 (0.00)	1.53 (0.04)	1.59 (0.10)
Pharmacoat 645	0.96 (0.01)	0.86 (0.03)	1.17[b]	1.45[b]
Pharmacoat 606[c]	1.06 (0.00)	0.84 (0.04)	1.30 (0.06)	1.43 (0.12)

[a] The values are the mean value of two determinations and values in brackets are the difference between the two determinations.
[b] One determination.
[c] The atomizer was cooled by water.

Table 3
Droplet size distribution of the liquid o/w-emulsions before spray drying and after reconstitution[a]

	Vaned wheel Rotation rate (rpm)				Rotary cup Rotation rate (rpm)			
	25 000		35 000		25 000		35 000	
	$d(v, 0.5)$ (μm)	SPAN	$d(v, 0.5)$ (μm)	SPAN	$d(v, 0.5)$ (μm)	SPAN	$d(v, 0.5)$ (μm)	SPAN
Liquid emulsion	0.98 (0.00)	0.98 (0.04)	0.96 (0.01)	0.99 (0.01)	0.97 (0.01)	0.99 (0.02)	0.94 (0.00)	0.96 (0.01)
	1.02 (0.01)	0.97 (0.02)	1.00 (0.00)	0.98 (0.00)	1.00 (0.01)	0.98 (0.01)	1.06 (0.01)	0.97 (0.03)
Reconstituted emulsion	1.13 (0.01)	1.43 (0.02)	1.17 (0.00)	1.71 (0.02)	1.20 (0.01)	1.73 (0.01)	1.12 (0.02)	1.99 (0.00)
	1.18 (0.01)	1.50 (0.00)	1.19 (0.04)	1.69 (0.02)	1.23 (0.01)	1.75 (0.05)	1.37 (0.03)	2.56 (0.03)

[a] The values are the mean value of two determinations and values in brackets are the difference between the two determinations. The experiment was performed with two replications.

dry emulsions was reduced from 56 to 24 μm by increasing the lipid content from 30 to 80%.

3.1.2. Dry emulsions with different HPMC types

The liquid o/w-emulsions with different HPMC types showed an almost identical droplet size distributions. As seen in Table 2, $d(v, 0.5)$ were about one micrometer and the SPAN-values were just less than 1, having a tendency to fall with an HPMC type of increased viscosity. During reconstitution, larger $d(v, 0.5)$ and SPAN values were obtained, especially for the reconstituted emulsion containing Pharmacoat 603.

3.2. Technical properties of the dry emulsions

Table 3 shows that $d(v, 0.5)$ were approximately 1 μm and the SPAN-values were below 1 for all the freshly prepared liquid o/w-emulsions.

For the reconstituted o/w-emulsions, lower SPAN-values down to 1.43 were obtained, applying the vaned wheel atomizer and/or a rotation rate at 25 000 rpm. The droplet size of the reconstituted o/w-emulsions was unaffected by neither the atomizer nor the rotation rate.

The porosimeter density for the dry emulsions was higher in the range of 0.261 up to 0.389 g/cm^3 at a rotation rate of 25 000 rpm, whereas the pycnometer density and the moisture content of the dry emulsions were unaffected by the two spray drying parameters. The pycnometer density was from 1.12 to 1.13 g/cm^3, and the moisture content in the dry emulsions was from 1.2 to 1.9%.

3.3. Stability of the dry emulsions upon ageing

The dry emulsions were able to reform the original o/w-emulsion after 6 months of storage in 75% relative humidity at ambient temperature and 40°C. During storage, the moisture content in the dry emulsions was slightly increased from 0.9 to 1.6% at ambient temperature and to 2.5% at 40°C. Fig. 1 shows that the outer structure of the dry emulsions was not changed after storage in 75% relative humidity at 40°C for a 6-month-period. The dry emulsions still consisted of well-separated spherical particles with shallow dents, seen to be deeper and more abundant in the smaller particles.

4. Discussion

4.1. Dry emulsions

It was possible to encapsulate up to 80% lipid with Pharmacoat 603 as a solid carrier. Dry emulsions having a lipid content up to 40% dry powder mass reformed the original o/w-emulsion upon reconstitution. Surface characterisation of the dry emulsions by electron spectroscopy for chemical analysis (ESCA) was performed as described previously (Pedersen et al., 1998). It showed that the surface composition of the dry emulsions corresponded to the composition of the formulation (data not shown).

HPMC types with different viscosity had no noticeable effect on the droplet size distribution of the reconstituted o/w-emulsion. When the viscosity was too high, the atomizer blocked due to thermal gelation.

By higher the liquid viscosity, the atomised droplet size increases resulting in a bigger particle size of the powder (Masters, 1991), explaining the variation in the particle size of the dry emulsions with different concentration of lipid and consequently different concentration of HPMC.

The spray drying process was optimised to dry liquid o/w-emulsions containing a high concentration of HPMC by reducing the temperature at the atomizer applying water-cooling. The experiments confirmed that by applying water-cooling at the atomizer, a smaller particle size and a better encapsulation of the lipid were obtained.

4.2. Technical properties of the dry emulsions

The type of rotary atomizer and the rotation rate had no noticeable effect on the technical properties of the dry emulsions containing 40% lipid.

The reconstitution properties of the dry emulsions were affected by both the type of rotary atomizer ($P < 0.01$) and by the rotation rate of the atomizer ($P < 0.05$), but during reconstitution, a monodisperse droplet size distribution was achieved.

The porosimeter density of the dry emulsions was affected by the rotation rate of the atomizer ($P < 0.05$). This is probably due to a particle size effect caused by the reduction of particle size with increased rotation rate of the atomizer (data not shown). Dry emulsions with small particles become more cohesive, having properties of low flowability and poor packing, explaining the lower porosimeter density seen at the high rotation rate.

The dry emulsions are cohesive powders having a poor flowability due to low density, the size and shape of the particles. The technical properties have to be improved for example by melt or wet granulation.

4.3. Stability of the dry emulsions upon ageing

In the storage period the dry emulsions were physically stable. After 6 months of storage the outer structure of the dry emulsions had not changed and the dry emulsions were able to reform the original o/w-emulsion after reconstitution in water. Dry emulsions having a lipid content of 40% dry powder mass present a potential for an oral drug delivery system.

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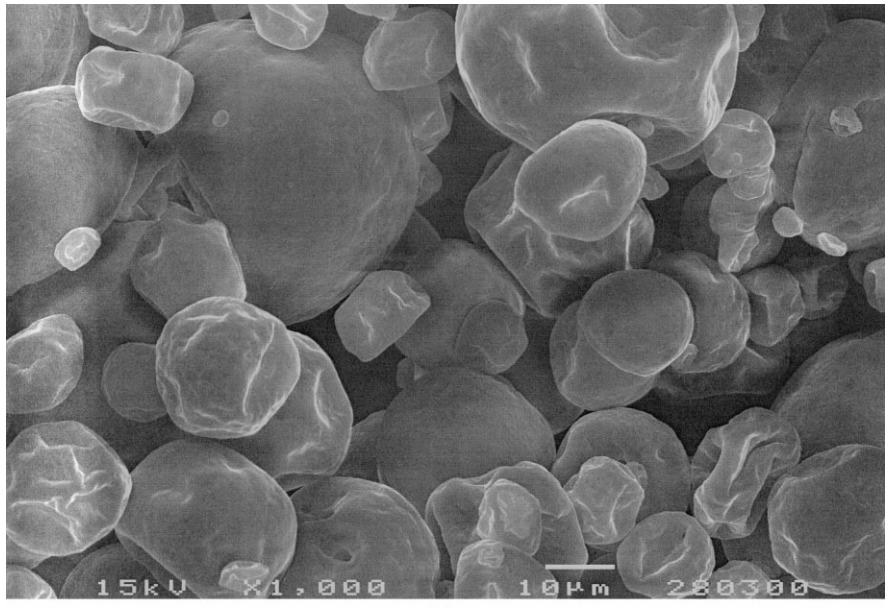

(a)

(b)

Fig. 1. Scanning electron micrograph of the dry emulsions; (a) before storage and (b) after 6 months of storage in 75% relative humidity at 40°C. Bar = 10 μm.

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