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Technical optimisation of redispersible dry emulsions

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Abstract

Preparation of dry emulsions suitable for tablet processing was examined in this study. Liquid o/w-emulsions were spray dried in a laboratory spray dryer applying hydroxypropylmethylcellulose (HPMC) as a solid carrier and emulsifier. As the lipid phase, fractionated coconut oil was used. The ability of various excipients to increase the density of dry emulsions was investigated. Adding sucrose to the formulation, redispersible dry emulsions with higher density were obtained. The type of rotary atomizer did not affect the dry emulsions containing sucrose nor the rate of rotation of the atomizer applied in the spray drying process. By wet granulation, using ethanol as a binder, free-flowing and compactable dry emulsions were obtained and simultaneously the reconstitution properties were preserved. It was concluded that dry emulsions could be optimised for tablet processing by wet granulation. Tablets having a lipid content up to 20% had proper tablet properties.

Keywords: Spray drying; Dry emulsion; Granulation; Tablet formulation; Redispersibility; Hydroxypropylmethylcellulose (HPMC)

1. Introduction

Dry emulsions are powders from which an o/w-emulsion can easily be reconstituted when exposed to an aqueous solution, and thus they present a potential for an oral drug delivery system (Christensen et al., 2000).

In literature, attention has mainly been paid to the design and preparation of dry emulsions, their stability (Christensen et al., 2000) and oral bioavailability (Nakamoto et al., 1975; Macheras and Reppas, 1986; Takeuchi et al., 1991; Shively and Thompson, 1995; Porter et al., 1996; Corveleyn and Remon, 1998b). The processing of dry emulsions into tablet and capsule preparations has drawn less attention. Tablets have been prepared as lyophilised dry emulsion tablets for buccal, sublingual and oral administration (Corveleyn and Remon, 1998a,b, 1999). For oral bioavailability studies, dry emulsions have been administrated as hard capsules (Takeuchi et al., 1991; Porter et al., 1996).

A previous study (Christensen et al., 2000) showed that physical stable dry emulsions having a lipid content up to 40% dry powder mass reform the original o/w-emulsion when exposed to an aqueous solution. Unfortunately the dry emul-

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sions turned out to be cohesive powders of poor flow properties.

The objective of the present study was to optimise the technical properties of the dry emulsions to make them suitable for tablet processing. Free-flowing and compactable dry emulsions, which reconstitute the original o/w-emulsion, were therefore desired. The study was performed by spray drying liquid o/w-emulsions containing fractionated coconut oil dispersed in aqueous solutions of low viscosity HPMC as described previously (Christensen et al., 2000). The dry emulsions were formulated with and without a density increasing excipient. The reconstitution properties and the tablet properties of the dry emulsions were investigated.

2. Materials and methods

2.1. Materials

2.1.1. Dry emulsions

Hydroxypropylmethylcellulose (Pharmacoat 603 and Pharmacoat 606) were supplied from Shin-Etsu, Japan. The viscosities of two polymers are 3.0 and 6.1 mPas (2% w/v solution) at 20°C, respectively. Fractionated coconut oil (Miglyol 812 N) was obtained from Condea, Germany. The following excipients were applied to increase the density of the dry emulsions: dextrin (Roquette, France), sucrose (Danisco Sugar, Denmark), colloidal silicon dioxide (Grace Davison, Gernamy), α-lactose monohydrate (DMV International, the Netherlands) and calcium hydrogen phosphate (Albright & Wilson, UK).

2.1.2. Granules

Ethanol 99.9% was purchased from Danisco Distillers, Denmark.

2.1.3. Tablets

Microcrystalline cellulose (Avicel PH 102) and cross-linked carboxymethylcellulose sodium (Ac-Di-Sol) were supplied from FMC International, Ireland.

2.2. Preparation of dry emulsions and granules

2.2.1. Dry emulsions

Five hundred millilitres of liquid o/w-emulsions were prepared as described previously (Christensen et al., 2000) with or without an excipient to increase the density of the dry emulsions.

The spray drying set up was as described previously (Christensen et al., 2000). The inlet air temperature was 120°C and the outlet air temperature was held at 75°C. In the spray drying process, water cooling of the rotary atomizer was applied.

2.2.2. Wet granulation

Two hundred g of granules was prepared manually with dry emulsions using ethanol as a binder.

2.3. Preparation of tablets

2.3.1. Compaction simulator

Three hundred and fifty to four hundred mg of dry emulsions were compacted in a compaction simulator (Pedersen and Kristensen, 1994; Sonnergaard, 1999) at pressures ranging from 57 to 133 MPa with 15.0 mm diameter flat faced punches. The compression profile was a simulation of an excentric press with a total process time of 2.2 s, corresponding to a contact time from 400 to 540 ms. depending on the material. Data were collected every 2.15 ms. The upper punch pressure was determined.

2.3.2. Fette Exacta I

Compaction of the dry emulsions was performed in an instrumented single punch Fette Exacta I tablet machine (Wilhelm Fette, Germany) equipped with 13.5 mm diameter flat faced punches with break mark. The pressure range was 18.3–90.9 MPa. The pressure was measured at the upper punch, and the signal was amplified and read on an oscilloscope screen.

2.4. Reconstitution of liquid o/w-emulsions

Reconstitution of liquid o/w-emulsions was performed by suspending 1.0 g of dry emulsion, 4.0 g

of granules or one tablet in 4.0 ml 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.

2.5. Storage of dry emulsions, granules and tablets

The dry emulsions, granules and tablets were stored in well-closed containers protected from light at ambient temperature and relative humidity.

2.6. Study design

By increasing the density of the dry emulsions and simultaneously preserve their reconstitution properties, it was attempted to improve the processing properties. Dry emulsions with 40% Pharmacoat 606 as the solid carrier were prepared applying five different excipients: dextrin, sucrose, colloidal silicon dioxide, lactose and calcium hydrogen phosphate. The lipid contents in the dry emulsions were from 30 to 50% of the dry powder mass. In the spray drying process, a vaned wheel atomizer with a rotation rate at 35 000 rpm was applied.

Subsequently compaction properties of the dry emulsions were investigated. Two dry emulsion types were selected (Table 1). Based on a complete 2^2 factorial experiment with two replications (Christensen et al., 2000), a rotary cup atomizer with a rotation rate at 25 000 rpm was applied in the spray drying process.

The effect of different compaction pressures on the reconstitution properties of the two dry emulsion types was investigated applying a compaction simulator. Forty to one hundred percent dry emulsion was mixed with water-soluble granules composed of 8% polyethylenglycol 6000 (Lutrol E 6000 from BASF, Germany) and 92% lactose anhydrate (Pharmatose DCL 21 from DMV International, the Netherlands) and subsequently compacted.

The two dry emulsion types were wet granulated using ethanol as a binder. To investigate the properties of the tablets containing dry emulsions, wet granulated dry emulsions were compacted in a Fette Exacta 1. Forty to seventy percent wet granulated dry emulsion was mixed with 25–55% Avicel PH 102 and 5% AC-Di-Sol and subsequently compacted.

2.7. Characterisation of liquid o/w-emulsions

The droplet size distribution of the o/w-emulsions before spray drying and after reconstitution of the dry emulsions, granules and tablets was determined by laser diffraction, Mastersizer S (Malvern Instruments Ltd., UK) (Christensen et al., 2000).

2.8. Density of dry emulsions

The dry emulsions were characterised by determining the density by helium pycnometry, AccuPyc 1330 (Micrometritics Ltd., UK) (Christensen et al., 2000).

2.9. Surface characterisation of the tablets

The outer macroscopic structure of the tablets was examined by scanning electron microscopy, JMS-5200 scanning electron microscope (Jeol, Japan) (Christensen et al., 2000).

Table 1
The composition of the two dry emulsion types selected for granulation and tablet formulation

Dry emulsion	Contents (%)			
	Miglyol 812N	Sucrose	Pharmacoat 603	Pharmacoat 606
I	40	–	60	–
II	30	30	–	40

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

Formulation containing: 40% Pharmacoat 606	Liquid emulsion		Reconstituted emulsion		Density
	d(v,0.5) (μm)	SPAN	d(v,0.5) (μm)	SPAN	(g/cm^3)
50% lipid & 10% dextrin[b]	1.41 (0.00)	0.92 (0.03)	1.98[c]	1.775[c]	1.10
40% lipid & 20% dextrin[b]	1.50 (0.01)	0.92 (0.00)	1.84 (0.02)	1.55 (0.04)	1.14
30% lipid & 30% dextrin[b,d]	1.45 (0.02)	0.95 (0.03)	1.71 (0.02)	1.25 (0.10)	1.20
30% lipid & 30% sucrose[b]	1.57 (0.06)	0.93 (0.05)	1.90 (0.00)	1.29 (0.00)	1.20
50% lipid & 10% colloidal silicon dioxide[e,f]	1.29 (0.00)	1.06 (0.06)	4.76 (0.57)	10.9 (2.0)	1.13
40% lipid & 20% colloidal silicon dioxide[e]	1.20 (0.03)	1.19 (0.17)	16.5 (0.91)	2.06 (0.11)	1.22
30% lipid & 30% lactose[b]	1.62 (0.01)	0.92 (0.00)	2.08 (0.05)	1.59 (0.01)	1.21
30% lipid & 30% calcium hydrogen phosphate[g]	2.37 (0.48)	27.8 (0.4)	2.20 (0.01)	5.78 (0.06)	1.27

[a] The values are the mean value of two determinations and the values in parentheses are the difference between the two determinations.
[b] Monodisperse droplet size distribution.
[c] One determination.
[d] The liquid o/w-emulsion was stable less than 1 day.
[e] Bidisperse droplet size distribution.
[f] Polydisperse droplet size distribution after reconstitution.
[g] Polydisperse droplet size distribution.

2.10. Tablet properties

Uniformity of mass, disintegration and friability of the tablets were determined according to the test methods described in Ph. Eur. A disintegration time less than 15 min and friability below one percent were accepted.

Subsequently the crushing strengths of tablets were determined, Schleuniger Tablet Hardness Tester model 6D (Schleuniger, Switzerland).

3. Results

3.1. Dry emulsions

Table 2 shows that monodisperse droplet size distributions were obtained for the liquid and reconstituted o/w-emulsions containing dextrin, sucrose and lactose. During reconstitution, the original o/w-emulsion was not fully reformed. The liquid o/w-emulsions containing 30% dextrin were stable for less than 1 day. Bidisperse and polydisperse droplet size distributions were obtained for the liquid and reconstituted o/w-emulsions containing colloidal silicon dioxide or calcium hydrogen phosphate, and the dry emulsions did not reform the original o/w-emulsion.

The pycnometer density of the dry emulsions was 1.10–1.27 g/cm^3 and was almost the same for the dry emulsions containing dextrin (30%), sucrose and lactose.

3.2. Stability against compression

Table 3 shows that for tablets containing up to 70% dry emulsion the compacted dry emulsions reformed the original o/w-emulsion to some extent during reconstitution in water. It was seen from the SEM photos (Fig. 1(a) and (b) and Fig. 2(a) and (b)) that the particle shape of the dry emulsions was the same before and after compaction.

3.3. Tabletting

Wet granulated dry emulsions reconstituted the original o/w-emulsion. The d(v,0.5) and the SPAN-value were 0.89 μm and 2.10 for granulated dry emulsion I and 1.37 μm and 1.49 for granulated dry emulsion II.

Table 3
Droplet size distribution of the liquid o/w-emulsions after reconstituting the dry emulsions and the tablets in water[a]

Formulation	Compaction pressure (MPa)	Reconstituted emulsion	
		d(v,0.5) (μm)	SPAN
Dry emulsion I	0	1.20 (0.01)	1.73 (0.01)
100% dry emulsion I	113.1	1.37 (0.03)	14.4 (3.8)
60% dry emulsion I	95.3	1.47 (0.07)	6.57 (0.43)
50% dry emulsion I	89.1	1.45 (0.02)	6.40 (0.29)
40% dry emulsion I	75.8	1.36 (0.01)	3.76 (0.27)
Dry emulsion II	0	1.68 (0.02)	1.41 (0.02)
100% dry emulsion II	109.6	1.81 (0.03)	24.8 (13.3)
70% dry emulsion II	74.8	1.78 (0.03)	4.64 (0.61)
60% dry emulsion II	82.9	1.75 (0.03)	3.48 (0.04)
50% dry emulsion II	57.2	1.76 (0.05)	3.11 (0.11)

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

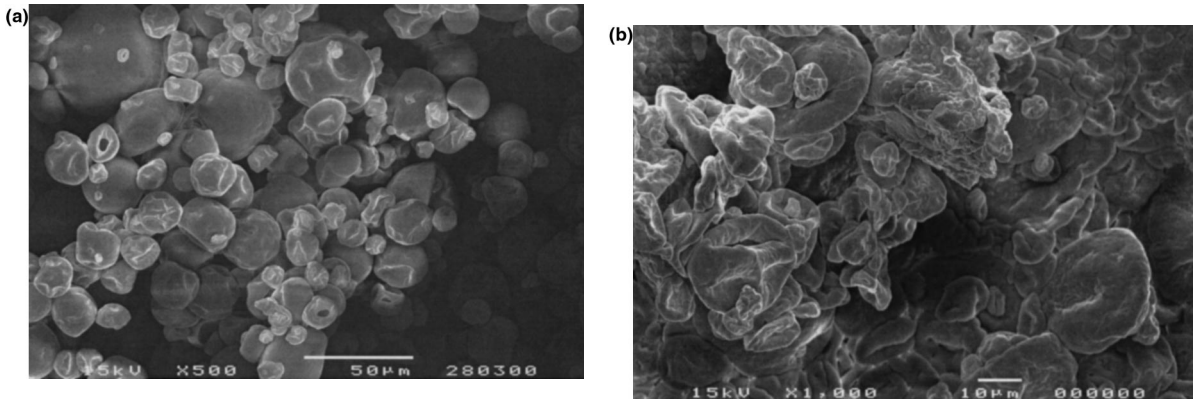

Fig. 1. Scanning electron micrograph of dry emulsion I; (a) pure dry emulsion (bar = 50 μm) and (b) a piece of a tablet containing 50% dry emulsion (compaction simulator). Bar = 10 μm.

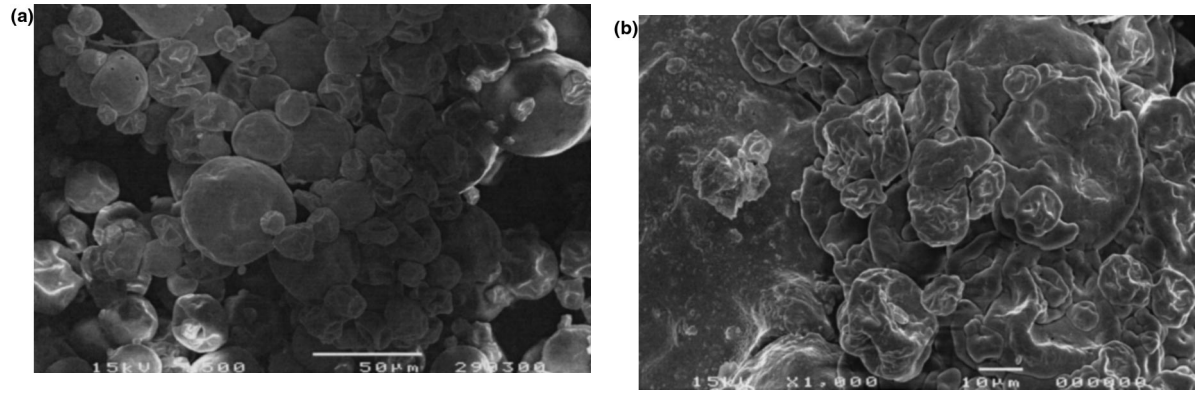

Fig. 2. Scanning electron micrograph of dry emulsion II; (a) pure dry emulsion (bar = 50 μm) and (b) a piece of a tablet containing 50% dry emulsion (compaction simulator). Bar = 10 μm

Table 4
Tablets containing wet granulated dry emulsion I[a]

	60% dry emulsion I, 35% Avicel PH 102, 5% Ac-Di-Sol	50% dry emulsion I[b], 45% Avicel PH 102, 5% Ac-Di-Sol	40% dry emulsion I, 55% Avicel PH 102, 5% Ac-Di-Sol
Compaction pressure (MPa)	81.8	87.2	63.5
Average of mass (g)	0.525 ± 0.04	0.404 ± 0.03	0.643 ± 0.05
Uniformity of mass	÷	+	+
Disintegration	+	+	+
Friability	+	+	+
Crushing strengths (N)	48 (3)	29 (8)	60 (11)
Lipid content (%)	24	20	16

[a] The values for average of mass are average value of 20 determinations. The values for crushing strengths are the mean value of four determinations and the values in brackets are the difference between the minimum and maximum determination. A cross is applied when the test for uniformity of mass, disintegration and friability were complied.
[b] Five percent talcum was added to the formulation to improve the flow.

Table 5
Tablets containing wet granulated dry emulsion II[a]

	70% dry emulsion II, 25% Avicel PH 102, 5% Ac-Di-Sol	60% dry emulsion II, 35% Avicel PH 102, 5% Ac-Di-Sol	50% dry emulsion II, 45% Avicel PH 102, 5% Ac-Di-Sol
Compaction pressure (MPa)	81.8	90.9	90.9
Average of mass (g)	0.419 ± 0.03	0.430 ± 0.03	0.482 ± 0.04
Uniformity of mass	+	+	+
Disintegration	÷	+	+
Friability	+	+	+
Crushing strengths (N)	37 (18)	36 (12)	64 (8)
Lipid content (%)	21	18	15

[a] The values for average of mass are average value of 20 determinations, the values for crushing strengths are the mean value of four determinations and the values in brackets are the difference between the minimum and maximum determination. A cross is applied when the test for uniformity of mass, disintegration and friability were complied.

Tablets containing wet granulated dry emulsion I had a lipid content from 16 to 24%. Table 4 shows results from tablets compacted at a pressure from 63.5 to 87.2 MPa and at crushing strengths from 29 to 60 N. During friability testing, the mass loss was below one percent and the tablets disintegrated within 15 min. The average of mass for the tablets was from 0.404 to 0.643 g, and the tablets containing 16 and 20% lipid comply with the uniformity of mass.

Tablets containing wet granulated dry emulsion II had a lipid content from 15 to 21%. As seen in Table 5, the compressing pressure was from 81.8 to 90.9 MPa and the crushing strengths from 36

to 64 N. The average of mass for the tablets was from 0.419 to 0.482 g, and the tablets comply with the uniformity of mass. During friability, the mass loss was within one percent and tablets containing 15 and 18% lipid were disintegrated within 15 min.

4. Discussion

4.1. Dry emulsion properties

The pycnometer density of the dry emulsions was increased slightly from 1.13 (Christensen et al., 2000) to 1.21 g/cm^3 by adding dextrin (30%), sucrose or lactose to the formulation containing 40% Pharmacoat 606 and 30% lipid. The reconstitution properties were preserved and a monodisperse droplet size distribution was obtained for the liquid and reconstituted o/w-emulsions.

The dry emulsions containing sucrose were chosen for further investigation in preference to the dry emulsions containing dextrin (30%) or lactose. Dextrin (30%) and lactose were excluded, because the liquid o/w-emulsions containing 30% dextrin were stable for less than 1 day, and because stability problems were reported for amorphous lactose (Fäldt and Bergenståhl, 1995, 1996a,b,c; Pedersen et al., 1998). The stability of amorphous sucrose should be improved by combining sucrose with a polymer in the form of a solid solution (Shamblin et al., 1996; Shamblin and Zografi, 1998).

Though the density was only slightly increased by sucrose addition, the dry emulsions were cohesive. The cohesiveness was, however, reduced compared to the dry emulsions containing 60% Pharmacoat 603 and 40% Miglyol 812N (Christensen et al., 2000).

The study showed that the spray drying parameters had no noticeable effect on the processing properties of the dry emulsions containing sucrose (data not shown). The pycnometer density ($P < 0.05$), the porosimeter density ($P < 0.01$), the moisture content ($P < 0.05$) and the particle size ($P < 0.001$) of the dry emulsions were affected by the type of rotary atomizer. Applying the vaned wheel atomizer, a higher density was obtained due to higher moisture content, and the higher moisture content was obtained due to a larger particle size, as larger particles require a longer drying time.

The particle size ($P < 0.001$) and the porosimeter density ($P < 0.05$) of the dry emulsions were also affected of the rotation rate of the atomizer. The particle size of the dry emulsions was increased with a low rotation rate and with larger particles, the dry emulsions become less cohesive, having better flow and parking properties, explaining the higher porosimeter density seen at low rotation rate.

4.2. Tablet properties

It was possible to granulate the two dry emulsion types (Table 1). The particle shape was intact and the reconstitution properties were preserved after wet granulation, and after compaction together with water-soluble excipients. It was assumed to be the same applying water insoluble excipients. It is simply impossible to measure the droplet size of the liquid o/w-emulsion without measuring the particle size of the excipients.

Tablets having a lipid content up to 20% had proper tablet properties and complied with all the tests. Tablets containing 21 and 24% lipid did not comply with the test for disintegration and uniformity of mass. To achieve full effect of Ac-Di-Sol, the compaction pressure had to be high. If higher pressures had been applied for the tablets containing 21% lipid, the tablets may have disintegrated within 15 min. The tablets containing 24% lipid did not comply with the uniformity of mass, because the proper flow properties were not preserved adding small amounts of Avicel PH 102.

The two dry emulsion types were also melt granulated (data not shown) and were able to reconstitute the original o/w-emulsion in water. Tablets containing melt granulated dry emulsions were prepared. The lipid content was only about 7.5–10% and the tablets did not comply with all the tests due to a high polyethylenglycol content, which was necessary to achieve granules. During compaction, the polyethylenglycol melted and stuck to the upper punch.

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