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Preparation of fenofibrate dry emulsion and dry suspension using octenyl succinic anhydride starch as emulsifying agent and solid carrier

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ABSTRACT

Purpose of this study was to investigate the ability of octenyl succinic anhydride (OSA) starch as emulsifier and solid carrier in dry emulsion (DE) and dry suspension (DS) formulations. Fenofibrate (FF) was loaded at lower and higher than its saturation concentration in oil phase to prepare the DE and DS by spray drying method. The DE and DS were successfully prepared with 36–48% and 46% production yield, respectively. After reconstitution in water, the emulsion with mean droplet size of 1–2 μm was obtained. Solid state characterization revealed the amorphous state of FF and the crystalline state of OSA starch in both DE and DS formulations. Both DE and DS enhanced FF dissolution rate compared to pure material and DS showed the highest dissolution rate. The DE and DS could be compressed to the tablets with acceptable disintegration time and without changeable dissolution profile. Moreover, the dissolution profiles of both DE and DS remained unchanged after 2 months storage at 40 °C.

1. Introduction

The lipid-based formulations, especially emulsified formulations, are potential strategies to increase the oral bioavailability of poorly water soluble drugs by increased dissolution rate or elimination of the dissolution step (Dollo et al., 2003; Hansen et al., 2004; Humberstone and Charman, 1997). DEs, which can be reconstituted when they are exposed to an aqueous solution, present the advantage to solve the thermodynamic instability of o/w emulsion and remain the improvement of bioavailability (Hansen et al., 2005, 2004; Jannin et al., 2008). The ability of DEs to increase the bioavailability has been confirmed by *in vivo* test for vitamin E acetate (Takeuchi et al., 1991), 5-phenyl-1,2-dithiole-3-thione (Dollo et al., 2003), 1-[4-[1-(4-fluorophenyl)-1-H-indol-3-yl]-1-butyl]spiro[iso-benzofuran-1(3H), 4 piperidine] (Lu 28-179) (Hansen et al., 2005), amlodipine (Jang et al., 2006), lovastatin (Ge et al., 2008), indomethacin (Hamoudi et al., 2012), and griseofulvin (Ahmed and Aboul-Einien, 2007).

DEs have been prepared by spray drying (Christensen et al., 2001a; Dollo et al., 2003; Hansen et al., 2004; Jannin et al., 2008), lyophilisation (Corveleyn and Remon, 1998) and rotary evaporation (Zu et al., 2014) in order to remove the aqueous phase of liquid o/w emulsion. After drying process, the dispersed lipid phase was encapsulated by solid carrier, which was water soluble such as trehalose, mannitol (Hansen et al., 2004), lactose monohydrate (Yin et al., 2009), hydroxypropyl methylcellulose (Christensen et al., 2001a; Hansen et al., 2005; Yin et al., 2009), dextrin (Jang et al., 2006; Yin et al., 2009), maltodextrin (Corveleyn and Remon, 1998) and water-insoluble carrier such as magnesium alumino metasilicate (Hansen et al., 2004). Conventional unit dosage forms such as tablets (Ahmed and Aboul-Einien, 2007; Christensen et al., 2001b; Corveleyn and Remon, 1998; Hansen et al., 2005, 2004) and capsules (Takeuchi et al., 1991) of DE have been prepared to earn more advantages in terms of dosing, handling, and patient compliance.

Octenyl succinic anhydride (OSA) starch is a modified starch produced by esterification process of starch and octenyl succinic anhydride. As a result of this modification, an amphiphilic structure is obtained from the hydrophilicity of starch and hydrophobicity of OSA (Sweedman et al., 2013). OSA starch has been used for many years, especially in food industry, as emulsifier, stabilizer, and encapsulating agent (BeMiller, 2009; Dokić et al., 2012; Sweedman et al., 2013; Tesch et al., 2002). In pharmaceutical field, OSA starch has been used in ophthalmic formulations as a new surface active polymer (Baydoun et al., 2004; Baydoun and Müller-Goymann, 2003) and in suspension (Kuentz et al., 2006).

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In this study, the ability of OSA starch as emulsifier and solid carrier in order to prepare DE without further emulsifier and solid carrier are investigated. DEs containing FF as poorly water soluble model drug were prepared by spray drying method. The amount of OSA starch was varied to investigate the effect of OSA starch concentration on the properties of liquid emulsion and DE. The amount of FF was loaded at lower and higher than its solubility in the oil phase. The obtained liquid emulsion and spray-dried powders were characterized for physicochemical properties in terms of particle size distribution, viscosity, morphology, solid-state property, density, and moisture content. Spray-dried powders were compressed by single punch tableting machine and investigated for tensile strength and disintegration. The dissolution behavior of spray-dried powders and tablet formulation was determined in 0.1% polysorbate 80 solution under non-sink conditions. Additionally, the stability of spray-dried powders regarding to the dissolution behavior were investigated.

2. Materials and methods

2.1. Materials

Octenyl succinic anhydride starch (Cleargum CO 03) was kindly donated by Roquette, Lestrem, France. Medium chain triglyceride (Miglyol® 812), castor oil, peanut oil, olive oil, soybean oil were supplied by Caesar & Loretz, Hilden, Germany. Fenofibrate was kindly donated from Merck Serono, Darmstadt, Germany.

For tablet preparation, powdered cellulose (Arbocel® P290, JRS Pharma, Rosenberg, Germany) was used as inert excipient. Crospovidone (Kollidone® CL, BASF SE, Ludwigshafen, Germany) was used as disintegrant. Colloidal silicon dioxide (Aerosil® 200, Degusssa, Frankfurt/Main, Germany) was used as glidant. Magnesium stearate (Parteck® LUB, Merck, Darmstadt, Germany) was used as lubricant.

Polysorbate 80 (Polysorbat® 80, Caesar & Loretz, Hilden, Germany) was used for dissolution medium preparation. Acetronitrile, HPLC-gradient grade and freshly prepared distilled water were used as HPLC mobile phase. All other reagents used were of analytical grade.

2.2. Solubility of fenofibrate in oil

The solubility of FF in the oils was determined by adding an excess amount of FF into the various oils. The mixtures were shaken at 25 °C with a constant rate of 100 rpm for 48 h to achieve the saturation concentration (SM 25 Shaker, Edmund Bühler, Hechingen, Germany). The samples were filtered with 0.45 μm syringe filter to remove the undissolved FF and diluted with ethanol for quantification of FF by ultraviolet–visible spectroscopy (Lambda 40, PerkinElmer, Rodgau-Juedesheim, Germany) at 338 nm. All tests were performed three times.

2.3. Preparation of dry emulsion and dry suspension

Firstly, blank emulsions, without FF, were prepared and investigated in order to find a stable formulation. The formulations of each blank emulsion are shown in Table 1. Only stable emulsions, which showed no phase separation at least 2 h after the preparation, were selected to prepare the FF emulsion. The aqueous phase containing OSA starch as emulsifier and solid carrier in the concentration range 10–30% w/w was prepared by dissolving OSA starch in distilled water. The oil phase was mixed with the aqueous phase at the ratios of 10–30% w/w and homogenized by a high speed colloid mill, Ultra-Turrax® (IKA Labortechnik, Staufen, Germany) for 10 min at 20,000 rpm. After obtaining stable emulsion formulations, FF was dissolved in the oil phase at the concentration approaching the saturation concentration of FF in the oil and prepared the emulsion with the same formulation and process used for the stable blank emulsion. Then, these emulsions were spray-dried with the Buchi mini spray dryer B-191 (Buchi, Flawil, Switzerland) under the following conditions: inlet temperature 150 °C, aspirator 80%, drying air flow rate 600 l/h, and feed rate 7.5 mL/min. The total solid content containing OSA starch, oil and FF in each formulation was 200–300 mg. The spray-dried powder was collected and kept in a desiccator prior to characterization. The production yield was calculated according to Eq. (1)

Table 1
Composition of blank emulsion formulations.

Formulation	Amount (% w/w)		
	Oil	Water	OSA starch
A	10.00	81.00	9.00
B	10.00	76.50	13.50
C	10.00	67.50	22.50
D	10.00	63.00	27.00
E	15.00	76.50	8.50
F	15.00	72.25	12.75
G	15.00	63.75	21.25
H	15.00	59.50	25.50
I	20.00	72.00	8.00
J	20.00	68.00	12.00
K	20.00	60.00	20.00
L	20.00	56.00	24.00
M	30.00	63.00	7.00
N	30.00	59.50	10.50
O	30.00	52.50	17.50
P	30.00	49.00	21.00

$$\%\text{production yield} = \frac{W_s}{W_t} \times 100 \quad (1)$$

where W_s is the weight of spray-dried powder and W_t is the total weight of OSA starch, oil, and FF.

FF suspension, containing 13.5% w/w OSA starch in the formulation was prepared and used to evaluate the effect of the FF loaded concentration. The amount of FF, which was 3 times above the saturation concentration, was dispersed in the oil phase. FF suspension was prepared by the same process as the emulsion. The suspension was spray-dried by spray dryer under the same condition as DE with continuous stirring by a magnetic stirrer.

2.4. Reconstitution of dry emulsion

About 100 mg of DE were dispersed with 10 mL of distilled water by hand-shaking, and then the emulsion was shaken for 10 min at 100 rpm (SM 25 Shaker, Edmund Bühler, Hechingen, Germany). The samples were withdrawn for determination of the droplet size distribution as described below.

2.5. Characterization of liquid emulsion

2.5.1. Droplet size distribution

The droplet size distribution of liquid emulsion before spray drying and after reconstitution was determined by laser diffraction with cuvette part (Sympatec, Clausthal-Zerllerfeld, Germany). The data was analyzed by using Fraunhofer theory. The emulsions were diluted with distilled water before the measurement. The droplet size was described by volume median diameter, $d(\nu,0.5)$. The SPAN value was calculated according to Eq. (2) and used to describe the width of the droplet size distribution.

$$\text{SPAN} = \frac{(d(\nu,0.9) - d(\nu,0.1))}{d(\nu,0.5)} \quad (2)$$