Powder Technology 271 (2015) 100–108

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Fabrication of spontaneous emulsifying powders for improved dissolution of poorly water-soluble drugs

Yotsanan Weerapol [a,b], Sontaya Limmatvapirat [a,b], Hirofumi Takeuchi [c], Pornsak Sriamornsak [a,b,*]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand
[b] Pharmaceutical Biopolymer Group (PBiG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand
[c] Laboratory of Pharmaceutical Engineering, Gifu Pharmaceutical University, 1-25-4 Daigaku-Nishi, Gifu 501-1196, Japan

ARTICLE INFO

Article history:
Received 17 July 2014
Received in revised form 24 September 2014
Accepted 26 October 2014
Available online 31 October 2014

Keywords:
Spontaneous emulsifying powders
Poorly water-soluble drugs
Dissolution
Solid carrier
Porous calcium silicate

ABSTRACT

The aim of the present study was to fabricate spontaneous emulsifying powders (SEP) for improving dissolution of poorly water-soluble drugs for oral drug delivery. The effect of drugs with different lipophilicity (log*P*), that is, nifedipine, felodipine, manidipine, and itraconazole on crystalline properties and dissolution profiles of SEP was also examined. The liquid spontaneous emulsifying formulation (SEF), composing of polyoxyl 35 castor oil, caprylic/capric glyceride and diethylene glycol monoethyl ether at a ratio of 1:1:8, was solidified with three different solid carriers, namely, fumed silica, porous silicon dioxide and porous calcium silicate (at 20%–50%). Porous calcium silicate at a concentration of 50% produced an excellent solid SEP formulation with the highest drug dissolution. The SEP formulations were free flowing with similar characteristics as that of liquid SEF. The differential scanning calorimetry and powder X-ray diffraction studies revealed the transformation of crystalline drugs (in pure drugs) to amorphous drugs (in the SEP formulations). This was further confirmed by scanning electron microscopy. Also, SEP containing 50% porous calcium silicate significantly improved the dissolution rate of all drugs tested due to the fast spontaneous emulsion formation and the decreased droplet size. Accordingly, this novel SEP formulation is the versatile and useful formulation that could be used to enhance the oral bioavailability of drugs by improving the dissolution of poorly water-soluble drugs.

1. Introduction

The oral route is the most convenient and preferred route of drug delivery as it offers a high level of patient adherence. However, more than 40% of drugs delivered via the oral route have limited therapeutic efficacy owing to poor aqueous solubility, which generally leads to poor oral bioavailability and high intra- and inter-subject variability [1]. Many formulation approaches have been employed to tackle the formulation challenges of poorly water-soluble drugs such as salt formation, complexation, solubilization, particle size reduction, nanosuspensions, solid dispersion [2,3]. The ability of nano-sized emulsions to improve the drug absorption in the gastrointestinal tract has also been demonstrated [4]. However, the use of emulsions in oral delivery was limited due to poor palatability, resulting from their lipidic composition, which may limit patient compliance. The advent of the spontaneous emulsification approach has reinstated the interest of researchers for examining application of emulsions for oral drug delivery. The self-emulsifying or spontaneous emulsifying formulation (SEF), an anhydrous form of emulsion, is isotropic mixture of natural or synthetic oils, solid or liquid surfactants and alternatively one or more hydrophilic solvents and co-solvents/co-surfactants [5,6]. SEF rapidly forms a fine oil-in-water emulsion (usually with droplet size between 100 and 300 nm) when exposed to aqueous media under conditions of gentle agitation or digestive motility that would be encountered in the gastrointestinal (GI) tract [7] and thus improves drug dissolution by providing a large surface area for partitioning of drug between oil and GI fluids [5,6].

However, the liquid SEF has limitations, for example, low drug loading capacity, low stability, drug leakage, interaction of SEF with capsule shell, etc. In order to overcome potential problems mentioned above, the liquid SEF is transformed into solid dosage forms. This combines advantages of SEF with those of a solid dosage form. Spray-drying and extrusion/spheronization techniques using silicon dioxide or fumed silica (e.g., Aerosil®) as a solid carrier have generally been employed to prepare solid dosage forms of SEF [8,9]. Most of the previous studies only focused on solid SEF prepared with silicon dioxide. In recent years, low density porous silica (e.g., Sylysia®) has been used for solidifying the SEF, in order to improve dissolution and bioavailability of poorly water-soluble drugs such as carvedilol [10], carbamazepine [11]. However, in this study, we intended to prepare so-called spontaneous emulsifying powders (SEP), a powder form of SEF, by physical mixing in mortar and pestle. This technique involved adsorption of the liquid

* Corresponding author at: Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand. Tel.: +66 34 255800; fax: +66 34 255801.
E-mail address: pornsak@su.ac.th (P. Sriamornsak).

http://dx.doi.org/10.1016/j.powtec.2014.10.037
0032-5910/

SEF onto solid carriers. The major advantage of using this technique is good content uniformity and high levels (up to 70% wt/wt) adsorption onto suitable carriers.

One of the limitations of conventional formulations is that different poorly water-soluble drugs behave differently in similar vehicles, thus underlining the need to assess candidate compounds on an individual basis. Previously, Araya et al. [12] examined the applicability of liquid SEF for the use to enhance the oral bioavailability of different poorly water-soluble compounds, in terms of emulsion droplet size after diluting in aqueous medium, emulsification rate and drug absorption in animal models. As far as we know, no published report has assessed the effect of physicochemical properties of different poorly water-soluble drugs on the dissolution behavior of SEP.

The primary objective of the present study was, therefore, to develop a novel SEP by physical mixing, using various percentages of three inert solid carriers, i.e., fumed silica (Aerosil® 200), porous silicon dioxide (Sylysia® 320) and porous calcium silicate (Florite® RE) (Table 1). Drug dissolution profiles of SEP using different solid carriers were compared and discussed in terms of surface area, particle size and porosity of solid carriers. The effect of drugs with different lipophilicity (log*P*), that is, nifedipine (NDP), felodipine (FDP), manidipine (MDP), and itraconazole (ITZ) on morphology, physicochemical properties and dissolution profiles of SEP was also examined.

2. Materials and methods

2.1. Materials

The surfactant, polyoxyl 35 castor oil (Cremophor® EL, referred to as P35) was supported by BASF (Thai) Co., Ltd. (Bangkok, Thailand). Caprylic/capric glyceride (Imwitor® 742, referred to as CCG) was purchased from Sasol (Hamburg, Germany). Diethylene glycol monoethyl ether (Transcutol® HP, referred to as DGE) was a gift from Gattefossé (Saint-Priest Cedex, France). Fumed silica (Aerosil® 200, referred to as FS) was supported by Evonik Industries (Hanua, Germany). Porous silicon dioxide (Sylysia® 320, referred to as PSD) was supported by Fuji Silysia Chemical, Ltd. (Aichi, Japan). Porous calcium silicate (Florite® RE, referred to as PCS) was a gift from Eisai R&D Management Co., Ltd. (Kobe, Japan). Nifedipine (referred to as NDP, log*P* 2.50) and felodipine (referred to as FDP, log*P* 4.46) were purchased from Xilin Pharmaceutical Raw Material Co., Ltd (Jiangsu, China). Manidipine dihydrochloride (referred to as MDP, log*P* 5.46) was supported by Sriprasit Pharma Co., Ltd. (Bangkok, Thailand). Itraconazole (referred to as ITZ, log*P* 5.66) was purchased from Nosch Labs Private (Hyderabad, India). The properties and chemical structure of the drugs studied are shown in Fig. 1. Distilled water was purchased from General Hospital Products Public Co., Ltd. (Pathum Thani, Thailand). Simulated gastric fluid USP without pepsin (SGF) is prepared by dissolving 2 g of sodium chloride and 7 mL of hydrochloric acid with distilled water to make a total volume of 1000 mL of solution. All other chemicals used in this study were of pharmaceutical grade and used as received without further purification.

2.2. Preparation of SEF and SEP

SEF was prepared, according to our previous report [13], by mixing of P35, CCG and DGE at a ratio of 1:1:8, at ambient temperature (25 °C) in light resistant container, until clear solution was obtained. Formulations were then loaded with NDP, at a concentration of 80 mg/mL (NDP-SEF). Various percentages of three inert solid carriers, i.e., FS, PSD and PCS (Table 1) were used to develop the novel SEP by mixing NDP-SEF with solid carriers (20%–50%) using mortar and pestle. Table 2 shows the composition of SEF and SEP formulations. To investigate the effect of drugs with different lipophilicity (log*P*), SEF was also loaded with FDP, MDP and ITZ, at concentration of 10 mg/mL, 15 mg/mL and 3 mg/mL, respectively, according to their solubility in SEF. SEF containing drugs was subsequently mixed with PCS (50%) to obtain drug-loaded SEP.

2.3. Determination of emulsion droplet size

SEF and SEP formulations were diluted with water or SGF (199 folds), and then kept for 2 h. Samples were centrifuged (666×*g*) for 10 minutes to remove the solid carriers. Sizes of emulsion were determined using photon correlation spectroscopy (model Zetasizer Nano ZS, Malvern, England).

2.4. Zeta potential measurement

The zeta potential of SEF and SEP formulations after dispersion in water or SGF (199 folds) was measured by zeta potential analyzer (model Zeta Plus, Brookhaven, USA) with an applied electric field of 1 V.

2.5. Surface free energy determination

The polarity and surface free energy (surface tension) of all SEP formulations were indirectly estimated through contact angle measurement ($n = 3$) which was carried out by sessile drop method using a drop shape instrument (model FTA 1000, Data Physics Corporation, USA). The percent polarity were determined based on proportion of polarity and surface free energy of all samples, their components and the contact angle measurement of two different standard liquids, which the values of surface free energy and their components were known, i.e., distilled water (72.8 mN/m) and formamide (58.2 mN/m) at 25 °C using Wu harmonic method equation [14].

$$\gamma_S^T = \gamma_S^D + \gamma_S^P \tag{1}$$

$$(1 + \mathrm{Cos}\ \theta)\gamma_s^T = \left[4\left(\gamma_S^D\gamma_L^D\right)/\left(\gamma_S^D + \gamma_L^D\right) + 4\left(\gamma_S^p\gamma_L^P\right)/\left(\gamma_S^p + \gamma_L^P\right)\right] \tag{2}$$

where γ_S^T is total surface free energy of solid surface, γ_S^p, is polarity force of solid surface and γ_S^p is dispersion force of solid surface. γ_L^P and γ_L^D are polarity and dispersion forces of standard liquid surface, respectively. θ is the contact angle of liquid formed on solid surface.

2.6. Morphology examination

The morphology of selected SEP formulations was investigated by a scanning electron microscope (model JSM-6510LV, Jeol, Japan) with an accelerating voltage of 15 keV. SEP samples were fixed on SEM stub with double-sided adhesive tape. All samples were coated, in a vacuum, with thin gold layer before investigation.

Table 1
Properties of solid carriers used in this study.

Solid carrier	Code	Surface area (m^2/g)	Particle size (nm)	Pore size (nm)	Oil adsorption (mL/100 g)
Fumed silica (Aerosil® 200)	FS	200	12	No pore	N/A
Porous silicon dioxide (Sylysia® 320)	PSD	300	3000	21	310
Porous calcium silicate (Florite® RE)	PCS	120	21,600	150	4,800

Note: N/A = not applicable.