Self-Emulsifying Pellets: Relations Between Kinetic Parameters of Drug Release and Emulsion Reconstitution—Influence of Formulation Variables

IOANNIS NIKOLAKAKIS, STAVROS MALAMATARIS

Department of Pharmaceutical Technology, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Received 17 November 2013; revised 3 February 2014; accepted 10 February 2014

Published online 4 March 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23919

ABSTRACT: The effects of surfactant type and content on the kinetics of emulsion reconstitution and release of drugs differing in lipophilicity from self-emulsifying microcrystalline cellulose pellets were studied. Furosemide and propranolol were the drugs, medium-chain triglyceride was the oil, and Cremophors ELP, RH40, and RH60 were the surfactants. Pellets were prepared by extrusion/spheronization with emulsions (75% water and 25%, w/w, oil/surfactant/drug). Stability of the emulsions was evaluated from changes in the back-scattered light, and re-emulsification and drug release from light transmittance and UV spectroscopy, respectively. Emulsion stability increased because of the incorporation of the drugs. Re-emulsification depended only on the surfactant content and was expressed by a simple power equation ($R^2_a > 0.945$, $Q^2 > 0.752$). Drug release was expressed by two biexponential equations ($R^2_a > 0.989$, $Q^2 > 0.699$ and $R^2_a > 0.947$, $Q^2 > 0.693$) implying initial burst and terminal slow release phase and by the linear form (Lineweaver–Burke) of Michaelis–Menten equation ($R^2_a > 0.726$, $Q^2 > 0.397$). Relationships exist between the rate constants of the equations describing emulsion reconstitution and drug release, for propranolol compositions ($R^2 = 0.915$), and for compositions of both drugs with less hydrophilic ELP and RH40 ($R^2 = 0.511$), and also, among dissolution efficiency, drug solubility in oil/surfactant, and emulsion reconstitution ability, indicating the importance of drug solubilization in oil/surfactant and re-emulsification ability on drug release. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1453–1465, 2014

Keywords: self-emulsifying; extrusion; spheronization; log *P*; solubility; surfactants; physical stability; light-scattering; dissolution rate; kinetics

INTRODUCTION

A major challenge in the formulation of poorly water-soluble drugs belonging to class II or class IV of the Biopharmaceutics Classification System (BCS) is the improvement of their solubility. A solution to this problem, among others, is the formulation of self-emulsifying drug delivery systems (SEDDS) consisting of a triglyceride lipid and a nonionic surfactant.[1] After arrival in the gastrointestinal (GI) tract, the SEDDS form spontaneously oil in water emulsions consisting of small, nanometer size range droplets, which present the drug at the absorption site of the epithelium, thus enhancing its permeability.

Self-emulsifying drug delivery systems, which may be liquid or semisolid or low melting solid, are usually transformed into solid dosage forms for stability improvement, easier handling, and lower production cost.[2] For this transformation, the simplest method is based on physical adsorption of the liquid or low melting lipidic SEDDS onto porous adsorbents by simple mixing.[3–6] Furthermore, freeze-drying or spray-drying after incorporation of SEDDS into hydrophilic or lipophilic solid carriers has been applied for a more efficient combination or even interaction between SEDDS and the carriers in spite of possible loss of SEDDS's ingredients during spray drying because of their low melting points.[7–10] The products of pharmaceutical self-emulsifying systems and carriers are usually filled into capsules as powder or free flowing granules or are compressed to tablets after mixing with suitable aids. Furthermore, formulation of SEDDS into double-layer tablets or tablets with osmotic core or loaded porous tablets has been reported, which however is a multistep laborious process.[11–14]

Recently, SEDDS have been incorporated into self-emulsifying pellets as granulation liquids before the extrusion/spheronization process and this method is gaining popularity, as demonstrated by the high number of recent publications.[15–20] Self-emulsifying pellets provide a multiunit dosage form with reduced dose dumping and local irritation, with improved distribution in the GI tract, independently of nutrition state.[21] Furthermore, in animals, self-emulsifying pellets have shown *in vivo* release of the incorporated drugs as if they were in the liquid emulsion and in certain cases improved bioavailability compared with marketed tablets.[16,18–20] Therefore, in the present work, self-emulsifying drug/oil/surfactant mixtures have been incorporated into microcrystalline cellulose (MCC) pellets and the effects of the formulation variables on the reconstitution of the emulsion and drug release from the self-emulsifying pellets were elucidated as they provide important information to formulators. In particular, attempt was made to elucidate the effects of drug lipophilicity (log *P*) and of surfactant type and content on: (1) the drug solubility in the oil/surfactant mixture, (2) the migration rate of the emulsions used in the preparation of pellets, and (3) the kinetics of emulsion reconstitution and of drug release from the pellets, in order to find possible relations between them.

Correspondence to: Ioannis Nikolakakis (Telephone: +30-2310-997635; Fax: +30-2310-997652; E-mail: yannikos@pharm.auth.gr)

Journal of Pharmaceutical Sciences, Vol. 103, 1453–1465 (2014)

According to literature, the optimal log *P* values of drugs added in self-emulsifying systems are between 2 and 4.[22] Therefore, furosemide (FS) and propranolol (PR) with different log *P* (2.0 and 3.5, respectively) but still within the range 2–4 were selected as the drugs. Also, the selected drugs represent two different BCS classes: class IV with low solubility/low permeability (FS) and class II with low solubility/high permeability (PR).[26,27] Consequently, any improvement of release in the gastric fluid due to the formulation into SEDDS could improve the drug absorption through redispersion into oil/surfactant droplets.[28] Additionally, PR has recently been recommended in low dose [1.5–2 mg/(kg day)] for children's therapies in hypertension, migraine, and recurrent primary epistaxis and suitable formulations are not available in the market.[29,30] FS was selected as a drug of low lipophilicity and also because of its reported solubility and permeability problems.[31] The optimal hydrophilic–lipophilic balance (HLB) range of surfactants for these systems was suggested to be 10–15 for finer droplet diameter and maximum drug release from SEDDS filled in soft gelatin capsules.[23,24] Therefore, three Cremophors of different hydrophilicity (HLB values between 13.9 and 15.7) and physical state (liquid or semisolid) were selected as the surfactants, employed at two oil/surfactant ratios (1.5 and 2.3) that were found to produce good pellets.[25] Consequently, as the SEDDS that were thus developed contained 60% or 70% oil and surfactants with HLB values within the range 13–16, they belong to type IIIA according to the Lipid Formulation Classification System.[1] Medium-chain triglycerides were the oil component of the self-emulsifying mixtures (SEMs) which, in combination with Cremophors, is known to improve oral drug absorption.[32]

MATERIALS AND METHODS

Materials

Microcrystalline cellulose (Avicel® PH-101, lot 6950C; FMC Ireland) was used as the pellet forming material. The drugs were FS (Batch 9033HRII) from Ipca (Mumbai, India; donated by Help Hellas, Athens, Greece) and PR base was prepared from hydrochloride salt as reported previously.[33] Medium-chain triglycerides of caprylic/capric esters; C_8: 59.6%, C_{10}: 39.9%, C_{14}: 0.4 % (Radia 7104; Oleon N.V., Oelegen, Belgium) and glyceryl polyethylene glycol ricinoleate (Cremophor ELP) or glyceryl polyethylene glycol oxystearate (Cremophors RH 40 and RH 60), donated by BASF (Ludwigshafen, Germany), were the components of the SEDDS. Distilled water was used as the external phase of the emulsions, for pellet preparation and reemulsification, and for the drug dissolution testing from the pellets.

Preparation of Pellets

Thirty grams of MCC powder was mixed with 30 g emulsion of 75% water and 25% (w/w) SEM (oil/surfactant/drug) for about 5 min massing time in a 1 L cylindrical mixing vessel, fitted with a three-blade impeller. Further addition of small amounts of 2–5 g of water (decided on the basis of preliminary trials) was required to obtain most spherical pellets. The apparently higher fraction of MCC (80%, w/w) in the formulations is because of the incorporation of the SEM as fluid liquid emulsion instead of viscous oily liquid after heating. Higher oil/surfactant/drug concentrations in the emulsion were not used to avoid possible emulsion instability. The resulting wet mass was extruded in a radial extruder (Model 20; Caleva Process Solutions, Dorset, UK) operated at 25 rpm and fitted with a 1 mm circular orifice and 1.75 mm thickness screen. The extrudate was immediately processed for 8 min in a spheronizer (Model 120; Caleva Process Solutions, Dorset, UK) fitted with a cross-hatch friction disc. The speed of rotation of the disc was 1360 rpm, determined with a flashing point type digital tachometer (accuracy +9 rpm; Control Ability Ltd., Blackburn, England), and, the corresponding linear perimeter speed of the disc (=2·π·disc radius·1360/60) was 8.55 m/s. The produced pellets were dried overnight in an air-circulation tray oven (UT6; Heraeus Instruments, Hanau, Germany) at 40°C and the dry pellets contained 20% SEM and 80% MCC.

Pellet Size, Shape, and Density

The pellets were characterized for size, shape, and density by using analytical sieves, image analysis, and helium pycnometry as described previously.[25] The produced batches had pellets of narrow size ranges (>80% in modal fraction 850–1200 μm), with mean diameters between 1000 and 1100, aspect ratios less than 1.1 and density between 1.4 and 1.44 g/cm^3. Therefore, pellet properties are not expected to affect drug release and emulsion reconstitution.

Solubility of Drugs in Oil/Surfactant Mixtures

Twenty-gram batches of optically clear liquids of oil/surfactant mixtures at ratios 1.5 (or 6:4, w/w) and 2.3 (or 7:3, w/w) were prepared by heating. Each batch was subsequently divided in two parts of 10 g that were respectively placed in closed vials at 37°C. Drug was added in steps of 10 mg in each vial and left to equilibrate until excess undissolved drug remained. The saturated solutions were centrifuged for 20 min at 3800 *g* (Heraeus Labofouge 400R; Thermo Electron Corporation, Osterode, Germany) to separate the undissolved drug and 50 μL aliquots of the clear supernatant was diluted with methanol to suitable concentration, and analyzed by UV spectroscopy (Shimadzu, model 700, Kyoto, Japan) at $\lambda = 275$ nm for FS and $\lambda = 290$ nm for PR. Clear liquids of oil/surfactant alone of the same ratio with those in the analyzed drug solutions were used as reference to account for any interference in the measured absorption. Solubility of the drugs in distilled water at 25°C and 37°C was also determined after equilibration for 24 h. All determinations were made in triplicates.

Stability of Emulsions Used for Pellet Preparation

The stability of the emulsions was evaluated using an optical analyzer (Turbiscan® MA Classic 2000; Formulaction, Toulouse, France) consisting of a near-infrared light source ($\lambda = 850$ nm) and two detectors: one that receives the transmitted light and a second that receives the light scattered at 135° angle. Ten milliliters of the emulsion was filled up to a height of 70 mm in a special flat-bottom cylindrical glass test tube sitting upright in the instrument holder and scanned at 40 μm intervals. Back scattering (BS%) versus height profiles were taken every 1 min. Changes appeared as BS% decrease with time near the bottom of the tube because of the depletion of oily droplets. For the determination of the migration rate, mid points of BS% in the depletion zones were selected and the heights corresponding to intersection of each curve with the line drawn parallel to *x*-axis from the selected BS% midpoints were plotted against the corresponding recording times