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European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 220–226
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Preparation and characterization of a self-emulsifying pellet formulation

Ahmed Abdalla, Karsten Mäder *

Department of Pharmacy, Martin Luther University, Halle/Saale, Germany

Received 28 June 2006; accepted in revised form 17 November 2006
Available online 29 November 2006

Abstract

The purpose of the current study is to investigate the feasibility of producing solid self-emulsifying pellets using the extrusion/spheronization technique. Pellets were made from a mixture of C18 partial glycerides, Solutol® HS15 and microcrystalline cellulose. Pellets with good physical properties (size, shape, friability) and self-emulsifying properties were produced. The pellets were, in contrast to pellets lacking Solutol, able to transfer a lipophilic dye and a spin probe into the aqueous media. The release kinetics and the microenvironment of the pellets during the release process were assessed using electron spin resonance (ESR) spectroscopy. The ESR results showed that the hydrophobic spin probe was localized mainly in the lipid environment all over the release time. Furthermore, the formulation was capable of accelerating the release of the drug diazepam and achieving a diazepam concentration above its saturation solubility.

In conclusion, spherical pellets with low friability and self-emulsifying properties can be produced by the standard extrusion/spheronization technique. The pellets are capable of transfering lipophilic compounds into the aqueous phase and have a high potential to increase the bioavailability of lipophilic drugs.

Keywords: Pellets; Extrusion/spheronization; Self-emulsifying drug delivery systems; Poorly water soluble drugs; Oral delivery system; ESR

1. Introduction

Nowadays, an increasing number of drugs are characterized by being poorly water soluble and highly lipophilic, resulting in a low and highly variable oral bioavailability. Due to this fact, many drug candidates fail to reach the market, although they exhibit potential pharmacodynamic activity. On the other hand, to achieve the desired plasma level, marketed poorly water soluble drugs are administered in higher doses than actually needed, leading to the rise of toxicity problems. Therefore, suitable formulation approaches need to be developed to improve solubility and bioavailability of poorly soluble drugs.

Strategies such as micronization, co-solubilisation, inclusion complexation [1], use of nanosuspensions [2], micellar solubilisation by surfactants, drug dispersion in carriers [3], and lipid-based formulations are presently employed to tackle the formulation challenges of poorly soluble drugs.

The use of lipid-based vehicles has generated considerable interest as a potential formulation approach to improve oral bioavailability of poorly water soluble drugs [4–6]. Lipid formulations are a diverse group of formulations with a wide variety of properties and usually consist of mixture of excipients, ranging from triglyceride oils through mixed glycerides, lipophilic surfactants, hydrophilic surfactants and cosolvents [7]. Lipid-based formulations can decrease the intrinsic limitations of slow and incomplete dissolution of poorly water soluble drugs by facilitating the formation of solubilised phases from which absorption takes place. The achievement of such phases will not essentially take place from the formulation itself, but alternatively from taking

* Corresponding author. Department of Pharmacy, Institute of Pharmaceutics and Biopharmaceutics, Martin Luther University, Wolfgang-Langenbeck Str. 4, D-06120 Halle (Saale), Germany. Tel.: +49 345 55 25167; fax: +49 345 55 27029.
E-mail address: Karsten.Maeder@pharmazie.uni-halle.de (K. Mäder).

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doi:10.1016/j.ejpb.2006.11.015

the advantage of the intraluminal processing to which lipids are subjected [8]. The extent of drug absorption from lipid vehicles is significantly affected by the dispersability of the administered lipid and drug. On the other hand, because of the inherent physical instability, the large volume of the two phase emulsion, and the poor precision of dose, the use of conventional emulsions is problematic. A formulation approach for avoiding such restrictive problems is the use of microemulsions or self-emulsifying drug delivery systems (SEDDS). The most famous example of a microemulsion-based system is the Neoral® formulation of Cyclosporine, which replaced Sandimmune® [9]. SEDDS have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs [10,11]. SEDDS are composed of a mixture of oil and a surfactant and they are capable of forming an O/W emulsion upon gentle agitation condition provided by gastrointestinal motion [7]. In such system, the lipophilic drug is presented in solution, in small droplets of oil, leading to the elimination of the dissolution step which can be the rate-limiting step in absorption of poorly water soluble drugs. SEDDS are usually formulated in a liquid form which has some disadvantages, especially in the manufacturing process, leading to high production costs. Furthermore, incompatibility problems with the capsule shell are common. The incorporation of the self-emulsifying mixture into a solid dosage form is desirable, but challenging, because self-emulsifying properties are harder to achieve with solid materials. However, the potential advantages of solid self-emulsifying dosage forms have attracted several authors [12,13].

Pellets have many advantages, over conventional solid dosage forms, making them of great interest to pharmaceutical industry. Flexibility in designing and developing the dosage form, and improving the safety and efficacy of bioactive agents are among these advantages. Due to the fact that pellets disperse freely in the gastro-intestinal tract, drug absorption is maximized with a subsequent reduction in peak plasma fluctuations and hence minimizing potential side effects without lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit time and therefore a reduction of intra- and inter-subject variability of plasma profiles is achieved. In addition, pellets reduce the problem of high local concentration of drugs and thus avoiding irritation that may be caused by certain active constituents [14].

The most widely used techniques for pellet production in the pharmaceutical industry are extrusion/spheronization (ES), solution/suspension layering, and powder layering. The process of ES has become the method of choice in the preparation of pellet-based dosage forms since it offers many technological advantages over the other methods, including the spherical shape with a narrow monomodal size distribution, good flow properties, low friability and uniform packing characteristics.

It is therefore very attractive to combine the advantages of self-emulsifying delivery systems with pellets. However, the development of self-emulsifying pellets is challenging, because high lipid loads often impair pellet formation. Using extrusion/spheronization, we focused our investigation on mixtures of mono- and di-stearate, Solutol® HS15 and MCC. Pellets were characterized for their size, shape, friability and dissolution. In addition, nitroxide loaded pellets were produced and the microenvironment within the pellets during the release process was monitored in an online process by the use of electron spin resonance (ESR) spectroscopy, since ESR is considered a powerful spectroscopic technique to monitor drug release processes non-invasively and continuously [15].

2. Materials and methods

2.1. Materials

Avicel PH 101 (Microcrystalline cellulose (MCC)) was purchased from FMC BioPolymer (PA, USA), and was used as the pellet forming material. Solutol® HS 15 (Macrogol-15-Hydroxystearate) was kindly provided by BASF AG, Ludwigshafen, Germany. Cithrol GMS® (C18 mono-and di-glycerides) was kindly provided by Croda GmbH, Nettetal, Germany. Tempolbenzoate (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl-benzoate, TB) and Tempol (2,2,6,6-tetramethyl-4-hydroxy-piperidin-1-oxyl, TL), were purchased from Aldrich Chem. Co., USA. Sudan®-red 7B dye was purchased from Riedel-de Haën AG, Germany. Diazepam was purchased from Fagron GmbH, Barsbüttel, Germany.

2.2. Methods

2.2.1. Preparation of pellets

The details of the composition of the dry ingredients of the formulations prepared are given in Table 1. The reference pellets were prepared by the same method used for the preparation of the self-emulsifying pellets.

2.2.1.1. Preparation of the self-emulsifying mixture. The preparation of the self-emulsifying mixture involved the following steps:

- Melting of GMS and Solutol at 70 °C.
- Dissolving the model drug, the dye or the spin probe in the molten blend.
- Addition of water to the molten lipid blend until a creamy mass is produced.
- Cooling to room temperature.
- Addition of the dry MCC and mixing in a kneader for 15 min.
- Further addition of water until a mass suitable for extrusion is obtained.

2.2.1.2. Extrusion/spheronization. The wet mass was extruded at 40 rpm in a radial screen twin-screw extruder (Fuji-Paudal, Japan) equipped with a die of 1-mm diameter circular openings and 1-mm thickness. The extrudate was