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Preparation of solid self-emulsifying drug delivery systems using magnesium aluminometasilicates and fluid-bed coating process

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ABSTRACT

Solid lipid-based drug delivery systems combine the advantages of solid dosage forms and the solubilizing potential of lipophilic vehicles. In spite of the fact that many methods were proposed for the solidification of liquid lipid formulations, there is no data on the application of the fluid-bed coating technique to impregnate porous pellets, containing magnesium aluminometasilicates with liquid self-emulsifying formulations. Moreover, the functionality of magnesium aluminometasilicates to form porous pellets by the extrusion/spheronization process has not been studied so far.

Therefore, the aim of the present work was to determine if magnesium aluminometasilicates could be incorporated into pellets in the extrusion/spheronization process and then to examine if such pellets may be used as solid cores for the conversion of liquid SEDDS into solid SEDDS (S-SEDDS) in the fluid-bed coating process. To achieve these goals, three grades of Neusilin namely SG2, US2 and NS2N were combined with MCC in three wt.% ratios i.e.: 30+70, 50+50, or 70+30. The results showed that the pellets whose matrix was composed of Neusilin SG2 had the highest porosity and the best mechanical resistance. The fluid-bed coating method was found suitable for the impregnation of the *placebo* pellets with liquid SEDDS, containing ibuprofen as an insoluble model drug. The amount of SEDDS adsorbed on the surface of pellets with silicates was from eight to fourteen times higher as compared to pellets without silicates. The morphology, diameter and circularity of pellets before and after the fluid-bed coating process was examined by scanning electron microscopy (SEM) and the automated particle characterization system (Morphologi G3). The pellets containing Neusilin SG2 had twice as high mechanical resistance as the pellets with Neusilin US2 or Neusilin NS2N, and they were suitable for fluid-bed processing. Dissolution studies showed that from the formulation composed of 70 wt.% of Neusilin SG2 after 45 min, more than 75% of ibuprofen was dissolved in water and after 30 min, more than 80% of ibuprofen was dissolved in the phosphate buffer. Similar results were obtained for S-SEDDS containing 70 wt.% of Neusilin US2. The sustained release of ibuprofen was found if 30 wt.% of Neusilin US2, 30–50% of Neusilin SG2, or 50–70 wt.% of Neusilin NS2N was incorporated into the matrix of pellets.

1. Introduction

Lipid-based self-emulsifying formulations have been developed with the aim to improve the solubility and bioavailability of poorly soluble drugs such as itraconazole, griseofulvin, cyclosporine or progesterone. Among them, the solid self-emulsifying drug delivery systems (S-SEDDS) are of a special scientific interest. The solidification of liquid SEDDS in the form of powder or microparticles gives the opportunity to prepare various solid dosage forms of improved efficacy, stability and patient compliance [1–3]. To achieve this goal, a detailed analysis of solid carrier properties during preformulation studies is necessary to predict the possibility of S-SEDDS preparation.

The application of inorganic excipients being derivatives of silicates for controlled drug delivery is an objective of several kinds of research [4,5]. Magnesium aluminometasilicates have been used as oral antacids due to their adsorptive properties. Silicates can also be applied for the design of tailor-made nanoparticles for modified drug release [6,7]. It was shown that the presence of magnesium aluminometasilicate in binary mixtures with ibuprofen improved the drug stability at high temperatures [8]. The relatively small size of ibuprofen molecule makes it one of the best model drugs to be incorporated into the channel network of silicate mesoporous structures [9]. It was reported that in synthetic mesoporous silicate materials, pore size distribution and pore shape were responsible for the controlled release of ibuprofen [5]. Co-grinding ibuprofen with silicates, such as kaolin, or mesoporous

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templated silica resulted in the amorphous form of the drug and improved its dissolution [4,7,10].

Liquid SEDDS can be converted into S-SEDDS by capsule-filling, spray-drying, melt granulation, melt extrusion/spheronization, incorporation in hydrophilic sponges, or adsorption on solid carriers [2,11]. S-SEDDS with gentamycin sulfate were prepared by adsorption of the drug on the surface of silicate particles [12]. It was shown that the application of Neusilin US2, Florite RE, or Sylysia 320 could be helpful to improve the bioavailability of gentamycin sulfate. PEG-8 caprylic/capric glycerides (Labrasol) were used as a nonionic self-emulsifying surfactant. Self-emulsifying powder was filled into hard gelatin capsules. Pharmacokinetic studies showed high plasma levels of gentamycin. S-SEDDS with furosemide in the form of microparticles were obtained by Zvonar et al. [3]. Pectin, calcium alginate and lactose were used as matrix-forming or shell-forming excipients in a vibrating nozzle technology. The authors claimed that self-emulsifying powder obtained could be filled into the capsule shell, agglomerated or compressed to form granules and tablets.

The advantages of pellets as a final solid oral dosage form or as a semi-product to prepare multiple unit dosage forms have been well-documented [13]. The plastic properties of microcrystalline cellulose (MCC) make this material an ideal excipient to prepare pellets by the extrusion/spheronization process [14]. However, such pellets do not disintegrate, which can cause delay in the dissolution of the drugs incorporated into the matrix core. Therefore, the functionality of lactose, dibasic calcium phosphate, barium sulfate, carrageenan, hypromellose, modified starch, pectin derivatives, hydroxyethylcellulose, crosspovidone, glyceryl monostearate, etc. as pelletization aids was investigated [15–17].

The application of the extrusion/spheronization method to prepare self-emulsifying pellets has been the objective of several kinds of research [2,18,19]. In general, liquid self-emulsifying formulation is used as a binder to prepare the plastic mass, and then to form pellets. Newton et al. [20] proposed the application of a self-emulsifying formulation as a surface active agent that facilitates wetting of MCC pellets. In the case of paracetamol, it was found that not only pellet composition but also their shape and surface properties influenced the drug release rate [21]. Abdalla and Mader [18] developed self-emulsifying pellets with diazepam by the extrusion/spheronization method. Pellet matrix was composed of glycerides, macrogol-15-hydroxystearate and MCC. Dissolution studies showed immediate diazepam release. Zhang et al. [22] proposed the preparation of self-emulsifying sustained-release pellets with puerarin. Liquid SMEDDS composed of the drug, castor oil, Cremophor EL and 1,2-propanediol was incorporated into the matrix of pellets composed of MCC and hypromellose. S-SEDDS containing dexibuprofen was also developed using Labrasol, Capryol 90 and Labrafil M 1944 C [23]. After the dilution of liquid SEDDS with ethanol, Aerosil 200 particles were suspended in the mixture, which was then spray-dried. The results of in vitro and in vivo studies showed that the dissolution and bioavailability of dexibuprofen increased.

However, there are no reports on the application of the fluid-bed coating process for the impregnation of inert porous pellets with liquid SEDDS to the best of our knowledge. The advantage of this process with regard to the impregnation of solid porous cores is the possibility of their heating and impregnation in one unit, which limits transfer losses. In general, the fluid-bed coating process can be automated after the optimization of critical process parameters, such as air temperature, air flow rate, atomizing pressure, pump output, bed load, etc. This can be important to assure the reproducibility of the method and to facilitate its scale-up.

Thus, the aim of the present study was to prepare S-SEDDS in the form of pellets that contained ibuprofen as a model drug. The fluid-bed coating method was used to convert liquid SEDDS into S-SEDDS. Porous pellets containing magnesium aluminometasilicate were prepared by the extrusion/spheronization process. Three different kinds of the silicate were combined with microcrystalline cellulose in three different weight percent ratios: 30+70; 50+50 and 70+30. The texture and mechanical resistance of *placebo* pellets were analyzed to determine if such pellets could be used in the fluid-bed coating process. Finally, the influence of the matrix composition on the properties of S-SEDDS, such as morphology, texture, drug content and drug dissolution kinetics was examined.

2. Materials and methods

2.1. Materials

Ibuprofen (IBU) was obtained from Shasun Chemicals and Drugs, India. Labrasol was supported by Gattefosse France. PEG 200 was purchased in Dow Chemicals, USA. Three different grades of magnesium aluminometasilicate i.e. Neusilin US2 (d_{true}=2.1843 g/cm^3), Neusilin SG2 (d_{true}=2.0942 g/cm^3), Neusilin NS2N (d_{true}=2.1503 g/cm^3) were kindly donated by Fuji Chemical Industry, Japan. Anhydrous lactose (d_{true}=1.5484 g/cm^3) and microcrystalline cellulose (MCC, Vivapur PH 101, d_{true}=1.5744 g/cm^3) were purchased from Sigma Chemicals Holland and JRS Pharma Germany, respectively. Distilled water was used as a wetting agent. Methanol of reagent grade was purchased from POCH Poland. Paraffin oil was obtained from Pharma-Cosmetic, Fagron Group Poland.

2.2. Preparation of placebo pellets

Nine formulations of *placebo* pellets containing magnesium aluminometasilicates, such as Neusilin US2, Neusilin SG2 or Neusilin NS2N, MCC and lactose were prepared by the extrusion–spheronization process (Table 1). Formulation F1 without magnesium aluminometasilicate was prepared as a reference.

Powders were blended and wetted in a mortar. Water was gradually being added for 3 min, then the plastic mass was being mixed for a further 3 min. The twin cylinder extruder Alexanderwerk GUN GA-65 (Germany) was used to prepare extrudates from the plastic mass. The plastic mass was extruded through the orifices of 1 mm in diameter. Extrudates were spheronized for 5 min using Caleva 120 (UK) spheronizer at a fixed rotation speed of 1400 rpm.

The pellets were dried in the ventilated oven (Premed type KCW-100, Poland) at 40 °C for 12 h, then they were sieved using a sieve shaker (CISA RP 08, Spain), equipped with a set of six sieves, i.e. 2000 μm, 1250 μm, 1000 μm, 800 μm, 600 μm, and 400 μm. The vibration was set at level 6, the sieving time was 15 min. Fraction of the sieve was calculated taking into account the percentage of pellets, remaining on each sieve.

2.3. Preparation of liquid SE formulation with ibuprofen

The solution containing 20 wt.% of ibuprofen was prepared in the mixture of Labrasol and PEG 200 in 1:1 ratio. Ibuprofen suspended in the solvent mixture was heated on the water bath (LW-2, SWL, Poland) at 50 °C while being stirred until the dissolution of the drug.

2.4. Preparation of S-SEDDS

Placebo pellets which passed through the sieve 2000 μm and remained on the sieve 1250 μm were impregnated with the liquid self-emulsifying formulation, using the laboratory fluid-bed coater Solidlab 1 (Bosch, Germany). A sample of 50 g of pellets was loaded on the bottom plate. The pellets were pre-heated at 50 °C for 15 min. The liquid self-emulsifying formulation was atomized by a nozzle of 0.8 mm in diameter, set at the bottom of the fluid-bed chamber. The pump output was 8%. The atomizing pressure was 1.2 bar. The microclimate was 203 mbar. The inlet temperature was 50 °C. The air flow in the fluid-bed chamber was set at 14 m^3/h to enable the homogeneous dispersion of pellets. The process was continued until the pellets started to agglomerate and remained at the bottom of the chamber. The amount of ibuprofen solution used for impregnation was determined