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Introduction of diffusing wave spectroscopy to study self-emulsifying drug delivery systems with respect to liquid filling of capsules

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ABSTRACT

The rheology of self-emulsifying drug delivery systems (SEDDS) is not thoroughly characterized these days. Since mechanical rheometers are often not well suited to study this kind of systems, there is need for novel physical methods. Several new optical techniques based on microrheology have recently made significant progress. We apply for the first time a specific microrheological technique called diffusing wave spectroscopy (DWS) to study different SEDDS. The obtained data were then correlated with the dosing precision of automated capsule filling.

As a result, the dynamic viscosities obtained from microrheology were in accordance with data from capillary viscosimetry. The DWS measurements revealed that all formulations had a clearly measurable storage modulus at frequencies >200 rad/s. Thus, all samples were low-viscous, while exhibiting non-Newtonian flow behavior. Obtained values of storage and loss modulus were then successfully correlated with the weight variability of capsules that were filled on a machine. In conclusion, the DWS technique enabled rheological analysis of self-emulsifying systems in a broad frequency range. The good data correlation with a capsule quality attribute was especially promising, since microrheological techniques are typically contact-free. Thus, they have a high potential in a quality by design framework of formulation development and production.

1. Introduction

There is an increasing interest in lipid-based formulations for oral delivery of biopharmaceutically challenging drugs (O'Driscoll and Griffin, 2008; Hauss, 2007; Porter et al., 2008). Different formulations typically range from simple oils to rather complex mixtures (Pouton, 2000, 2006). The more elaborate formulations are often self-emulsifying upon contact with aqueous fluids. Very fine dispersions are formed spontaneously in this way. Depending on the evolving particle size, self-emulsifying drug delivery systems (SEDDS) are differentiated from self-microemulsifying systems (SMEDDS). This dispersion behavior is a characteristic for the formulation even though the final particle size is *in vivo* further affected by the digestion process (Fatouros and Mullertz, 2008; Dahan and Hoffman, 2008).

Apart from the particle size upon dispersion, the rheological properties of the system are important. They define the mechanical behavior of the formulation, which is of technical as well as of biopharmaceutical relevance. Rheological properties are critical for the filling of soft or hard capsules and from a biopharmaceutical perspective, any viscous formulation has to facilitate water penetration sufficiently, before any dispersion can occur (Kuentz, 2011). It is of general interest to correlate such material properties with quality attributes of the final dosage form. This is also an objective of the quality by design (QbD) initiative, in which formulations as well as manufacturing processes are especially designed to ensure a predefined quality (Yu, 2008). A part of the QbD research aims to better characterize materials and formulations to subsequently study their effects on targeted product quality attributes. Specifically new characterization methods such as DWS are needed for a deeper rheological assessment of SEDDS or SMEDDS.

Groves and Galindez (1976) were pioneers in rheological analysis of self-emulsifying oil/surfactant systems. They measured flow curves and found a relation between viscosity and the ease of self-emulsification. Systems with good spontaneity were characterized by a decreasing viscosity at maximal shear rate as the water concentration was increased. In the following years, viscosity was often not considered in studies on self-emulsifying systems. In some cases, only a single viscosity value was reported (Shafiq-un-Nabi et al., 2007; Kadu et al., 2011). Because the formulations may not exhibit Newtonian flow behavior, such results must be handled with care. A more detailed rheological analysis was conducted

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by Biradar et al. (2009), who used oscillatory rheology to study the self-emulsification process. Hydration of the formulation produced intermediate liquid crystalline phases that demonstrated visco-elastic flow behavior. Interestingly, recent studies on diluted O/W microemulsions showed that the evolving low-viscous fluids displayed non-Newtonian flow characteristics with shear thinning (Djekic et al., 2011; Zheng et al., 2011). This was a remarkable result, since a microemulsion with an inner phase of discrete particles would be expected to exhibit Newtonian flow behavior. It was therefore assumed that particle interactions were leading to micelle aggregates or the formation of other colloidal structures that resulted in non-ideal flow behavior.

This differentiation of low-viscous Newtonian from non-Newtonian flow is particularly important for undiluted SEDDS or SMEDDS. Filling of rather low-viscous formulations into hard capsules can lead to loss of filling mass due to splashing around the dosing nozzle of the machine. This typically increases the rate of leaking capsules as well as the weight variability of the units. The phenomenon was recently studied with different pharmaceutical oils to predict a ranking of capsule filling adequacy based on Newtonian viscosity and surface tension (Niederquell and Kuentz, 2011). In a next research step, the capsule filling of simple mixtures and more complex formulations, such as SEDDS or SMEDDS, should be investigated.

Currently, knowledge about the rheological properties of pharmaceutical self-emulsifying systems is rather limited. These fluids are not only mixtures of surfactants, oils, and co-solvents but they often comprise additional polymers. Thus, the characterization of mechanical properties in a broad range of frequencies should be very interesting. However, such oily and low-viscous fluids are not easy to measure using a typical controlled-stress rheometer. Oscillatory measurements of such fluids are conducted at a very low shear to stay in the linear visco-elastic range. Measurement accuracy is one issue in these conditions and another is the typical upper limitation of the angular frequency range in oscillation ($\sim$100 rad/s). Higher frequencies are, however, of interest for any process that involves a high shear such as the liquid filling of capsules.

Recent advances in microrheology have improved the capability to investigate complex fluids (Waigh, 2005). Among these techniques, the DWS is particularly interesting and review articles outline the measurement principle (Harden and Viasnoff, 2001; Alexander and Dalgleish, 2007; Corredig and Alexander, 2008; Lopez-Diaz and Castillo, 2011). DWS is an optical technique based on light scattering similar to the well-known dynamic light scattering (DLS). In both cases, intensity fluctuations of scattered light provide information on the dynamics of the light-scattering particles. However, the purpose of DLS is to measure particle size by determining the diffusion coefficient of the particles in a fluid with a given viscosity. DWS, on the other hand, investigates microrheological properties of a fluid based on the mean square displacement of the particles (MSD). The particles can occur naturally in the sample or they are simply added as defined tracer particles. It is important to note that traditional DLS and DWS differ greatly in their number of light scattering events. DLS requires single scattered light for a valid measurement. Therefore only diluted systems are measured or special techniques are employed to suppress "multiple scattering". DWS, in contrast, requires multiple scattering as the calculation of the MSD is based on the assumption that light propagation in the sample can be described as a diffusion process.

Principles of DWS were established in the late 1980s but the development of instrumentation and further theoretical understanding were needed to make the method applicable. To the best of our knowledge, DWS has so far not been used to investigate any pharmaceutical mixture for capsule filling.

The primary aim of this study is to introduce DWS for the characterization of self-emulsifying formulations. Eight typical systems are studied here and DWS microrheological viscosity is compared with values obtained from capillary rheometry. First the dilution behavior is studied by DLS, which allows classification by size. The microrheological method DWS is then used for the first time to characterize the different pharmaceutical formulations. Lastly, an attempt is made to use these rheological results for a correlation with capsule weight variability that is obtained from an automated filling process.

2. Materials and methods

2.1. Materials

The medium-chain triglyceride oil Miglyol® 812 was received from the local vendor Hänseler AG (Herisau, Switzerland). The medium-chain partial glycerides Imwitor® 742 was purchased from Sasol (Witten, Germany), whereas Tween® 80 (polysorbate 80) as well as the hydrophilic polymer polyethylene glycol 400 were obtained from Sigma–Aldrich Ltd. (Buchs, Switzerland). The surfactants Cremophor® RH40 (polyoxyl 40 hydrogenated castor oil), Cremophor® EL (macrogol glycerol ricinoleate 35), and Solutol® HS15 (macrogol 15 hydroxystearate) as well as the viscosity enhancer Kollidon® 30 (1-ethenyl-2-pyrrolidinone homopolymer) were excipients from BASF AG (Ludwigshafen, Germany). Gattefossé (Lucerne, Switzerland) kindly supplied Maisine® 35-1 (glycerylmonolinoleate), Labrasol (caprylocaproylmacrogolglycerides), and Transcutol® P (diethylene glycol monoethyl ether). The emulsifier Capmul® MCM (glyceryl mono-dicaprylate) was obtained from Abitec Corp. (Janesville, USA) and ethanol (absolute) was purchased from J.T. Baker (Deventer, the Netherlands). All excipients were used as supplied without any further purification.

We used Licaps® hard gelatin capsules of size I Capsugel (Bornem, Belgium). Glass cuvettes (5 mm) as well as the titanium dioxide tracer particles (mean diameter 360 nm) were obtained from LS Instruments AG (Fribourg, Switzerland). The polystyrene NIST standard (600 ± 0.30 nm) was purchased from Polysciences Europe Ltd. (Eppelheim, Germany).

Artificial intestinal medium (FaSSGF) was prepared using the digestive enzyme pepsin from Hänselerplc (Herisau, Switzerland) together with sodium taurocholate (PCA S.p.A., Basaluzzo, Italy), sodium chloride from Sigma–Aldrich Ltd. (Buchs, Switzerland) and Lipoid S100 (94% phosphatidyl choline) from Lipoid Ltd. (Ludwigshafen, Germany). Finally, hydrochloric acid (1 N) was added to the medium for adjustment of the pH value (1.6).

2.2. Preparation of self-emulsifying systems

The batches were prepared with a total batch size of 250 g for each formulation and the oily phase was mixed before the surfactant was added. Semi-solid excipients, such as Cremophor® RH40 and Imwitor® 742, were initially melted. One formulation comprised the additive polyvinylpyrrolidone K30 and this mixture required additional stirring for 12 h at 45 °C. Formulations with a co-solvent were prepared by adding this excipient in a last compounding step. The final mixture was visually assessed to assure that a single phase was obtained. Subsequently, the formulations were filled in hermetically sealed vials. All formulation compositions are listed in Table 1 by giving amounts in %(w/w).

2.3. Particle size analysis of diluted samples

A Zeta Sizer Nano-ZS from Malvern Instruments Ltd. (Malvern, United Kingdom) was used to determine particle size by means of DLS. This device employed a 4 mW He–Ne laser with a wavelength