Introducing Diffusing Wave Spectroscopy as a Process Analytical Tool for Pharmaceutical Emulsion Manufacturing

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ABSTRACT: Emulsions are widely used for pharmaceutical, food, and cosmetic applications. To guarantee that their critical quality attributes meet specifications, it is desirable to monitor the emulsion manufacturing process. However, finding of a suitable process analyzer has so far remained challenging. This article introduces diffusing wave spectroscopy (DWS) as an at-line technique to follow the manufacturing process of a model oil-in-water pharmaceutical emulsion containing xanthan gum. The DWS results were complemented with mechanical rheology, microscopy analysis, and stability tests. DWS is an advanced light scattering technique that assesses the microrheology and in general provides information on the dynamics and statics of dispersions. The obtained microrheology results showed good agreement with those obtained with bulk rheology. Although no notable changes in the rheological behavior of the model emulsions were observed during homogenization, the intensity correlation function provided qualitative information on the evolution of the emulsion dynamics. These data together with static measurements of the transport mean free path (l^*) correlated very well with the changes in droplet size distribution occurring during the emulsion homogenization. This study shows that DWS is a promising process analytical technology tool for development and manufacturing of pharmaceutical emulsions. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3902–3913, 2014

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INTRODUCTION

Emulsions have a wide range of applications in a plethora of fields, from which we can highlight the food, cosmetic, and pharmaceutical sciences.[1–3] These dispersions of two or multiple liquid phases are generally stabilized by a single or several emulsifiers, for example, surfactants, amphiphilic polymers, or small particles. However, when used for the above-mentioned applications, the emulsion composition often comprises several other additives, which introduce a high degree of complexity to the emulsion structure.

To fine-tune the final structure of an emulsion product, it is essential to understand the physical interactions between the different emulsion components as well as the influence of the different processing steps on, for example, the emulsion structure or stability. Therefore, it is of major interest to analytically follow the process of emulsion manufacturing (e.g., homogenization). This aim is in line with the initiatives of "Quality by Design" (QbD) and Process Analytical Technologies (PAT) that are being increasingly implemented to improve product and process understanding as well as quality control.[4,5] The QbD approach identifies critical quality attributes and studies how they are correlated with critical material and process parameters. On the basis of such knowledge, a PAT strategy can be defined to monitor the manufacturing process regarding final product quality.

The complex interactions between the different components in the emulsions have been characterized with, for example, light scattering, rheology, microscopy, and turbidity measurements.[2] Although some of these techniques can only be used offline, that is, to characterize the final product, others have some potential for real-time monitoring. Especially for process analytics, a technical hurdle is often the high turbidity of typical pharmaceutical emulsions. Herein, the most suitable techniques to monitor changes during emulsion manufacturing would be rheological analysis, or other techniques that allow measurements at high turbidity, such as Raman spectroscopy,[6] dielectric spectroscopy,[7] ultrasound techniques,[8] or diffusing wave spectroscopy (DWS).[9]

The assessment of the rheological properties is of high importance when characterizing emulsions, because detailed information about the flow behavior, emulsion structure, as well as the nature and strength of the interactions between droplets can be obtained.[10–12] The use of mechanical rheometers allows the study of mechanical emulsion properties on a macroscopic scale. Texture and flow properties can be measured through the stress-induced deformation of the samples. Although these properties are also used to assess the emulsion structure, the bulk rheological measurements are often not sensitive to important local changes in the microstructure. Thus, to assess the interactions between the different emulsion components and the variations in emulsion microstructure, microrheological techniques are best suited.[13]

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Several techniques have been used to measure the microrheology of samples, such as single- or multiple-particle tracking microrheology, atomic force microscopy, dynamic light scattering (DLS), and DWS,[13] where mainly the latter has a potential for real-time process analytics. DWS is a powerful optical technique specifically suited to study turbid samples. The method is based on the analysis of the fluctuations of coherent laser light that is scattered multiple times within a sample.[14,15] DWS is a fast method where the sample is probed by a laser beam over a large frequency range that is partially inaccessible to classical mechanical rheology. These characteristics, together with the ability to measure a sample in its natural unperturbed state, make DWS well suited for on-line measurements in a flow-through cell.

Diffusing wave spectroscopy is an advanced light scattering technique with a well-founded theoretical background,[14,16] which was originally introduced to study highly concentrated colloidal systems.[17,18] This technique is being increasingly employed in the field of food science,[2,9] for instance, to follow gelation or acidification,[19,20] as well as to monitor destabilization mechanisms, such as flocculation and/or creaming or Ostwald ripening.[21–23] DWS has only recently been introduced into the pharmaceutical field,[24] but to the best of our knowledge not for monitoring of a pharmaceutical manufacturing process.

In this article, DWS was employed as an at-line technique to monitor the manufacturing process of pharmaceutical emulsions. The selected model system was a simple oil-in-water (O/W) pharmaceutical emulsion that was stabilized with a nonionic surfactant and different concentrations of xanthan gum. The evolution of the emulsions during the manufacturing process was investigated using DWS and was complemented with offline mechanical rheology and microscopy analysis. The results obtained were compared with near-infrared (NIR) analytical centrifugation that was used for offline stability testing.

MATERIALS AND METHODS

Materials

Xanthan gum, Vanzan NF-C, was supplied by Vanderbilt Minerals, LLC (Norwalk, Connecticut) and almond oil was purchased from Henry Lamotte Oils (Bremen, Germany). Polysorbate 80 (i.e., polyoxyethylene 20 sorbitan monooleate), methylparaben, and propylparaben were obtained from the local supplier Hänseler (Herisau, Switzerland). All excipients were used as supplied without any further purification.

Methods

Emulsion Preparation

The stock solutions for the continuous emulsion phase were prepared by dissolving 2.0% (w/w) xanthan in distilled water containing preservatives while stirring for 48 h. The solution containing preservatives was prepared by dissolving 0.1% (w/w) propylparaben and 0.5% (w/w) methylparaben at 60°C in distilled water. The aqueous phase was prepared by diluting the stock solution to the desired xanthan concentration (0.5%–1.0%, w/w) with the solution containing preservatives. Two-hundred gram of this phase were heated to 50°C and further mixed with a Polytron homogenizer (PT10–35 GT; Kinematica, Luzern, Switzerland) at maximal speed. The oil phase was prepared by mixing 2.0 g of polysorbate 80 with 30.0 g of almond oil, and heating to 50°C. The oil phase was then added to the aqueous phase while homogenizing. The homogenization process was continued and samples of 12 g were taken at specific time intervals. The total homogenization duration was 10 or 17 min, depending on the final concentration of xanthan gum in the aqueous phase, that is, 0.45% (w/w) or 0.68% and 0.90% (w/w), respectively.

The obtained samples were characterized at a temperature of 25°C using bright field (BF) microscopy, confocal microscopy, mechanical rheology, DWS, and NIR analytical centrifugation.

BF Microscopy

An Olympus CKX41 microscope (Tokyo, Japan) was used for BF analysis. A small amount of sample was placed on a microscope slide followed by gentle squeezing with a cover slip. To obtain the droplet size distributions, the diameters of approximately 100 oil droplets were analyzed from recorded images using the public domain image analysis software ImageJ (National Institutes of Health, USA). The following bins were used for the droplet size distribution histogram: 0–1, 1–2, 2–3, 3–5, and 5–10 μm. The bins were normalized for the total surface of the histogram to become unity.

Confocal Microscopy

For confocal microscopy, an Olympus FluoView 1000 system was employed. The instrument configuration was based on an inverted Olympus IX61 microscope equipped with a 488 nm laser and a 40x objective with numerical aperture of 0.90. For these experiments, the samples were stained with the lipophilic dye Nile Red. A droplet of the sample was thereafter placed on a cover slip and confocal images were recorded in the bulk at approximately 15 μm from the interface between the cover slip and the sample.

Mechanical Rheology

Mechanical rheology, which allows to probe the bulk rheology of the samples, was performed on a Bohlin Gemini rheometer (Malvern Instruments Ltd., Malvern, UK) equipped with sand blasted plane-cone geometry (60 mm, 2°) and a solvent trap. The storage, G', and loss moduli, G'', were measured in oscillation mode with a constant strain amplitude of 0.05. This value was found to be in the linear viscoelastic range based on the results of an amplitude sweep at 1 Hz.

Diffusing Wave Spectroscopy

Theory and Experimental Setup. Diffusing wave spectroscopy is a multiple light scattering technique that requires highly turbid samples to ensure that the propagation of light in the sample can be approximated by the diffusion equation. In this work, a DWS RheoLab (LS Instruments AG, Fribourg, Switzerland) was used for diffusing wave spectroscopic analysis in transmission mode. A scheme of the apparatus is illustrated in Figure 1.

The laser light ($\lambda = 685$ nm) was scattered from a ground glass and collected by a single lens before illuminating the turbid sample. To avoid time-consuming measurements at comparatively low frequencies, that is, long lag times in the intensity correlation function (ICF), the instrument employed the so-called echo technique.[25,26] The echo data complemented the light scattering results to obtain a complete ICF over a broad range of lag times. In echo mode, the ground glass rotates and