International Journal of Pharmaceutics 484 (2015) 85–94

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Thorough characterization of a Self-Emulsifying Drug Delivery System with Raman hyperspectral imaging: A case study

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ARTICLE INFO

Article history:
Received 23 December 2014
Received in revised form 19 February 2015
Accepted 21 February 2015
Available online 23 February 2015

Keywords:
Hyperspectral imaging
Raman spectroscopy
Self-Emulsifying Drug Delivery System
Particle size
PAT tool

ABSTRACT

Newly developed drugs often have poor bioavailability due to their poor water solubility (BCS class 2 drugs). It is therefore necessary to develop new strategies to enhance their solubility and their activity, among which, Self-Emulsifying Drug Delivery System (SEDDS). The efficacy of the drugs contained in these preparations is mainly affected by the solid state and the particle size of the active pharmaceutical ingredient (API).

However, it is quite complex, long and expensive to characterize these parameters with classical techniques such as X-ray powder diffraction, differential scanning calorimetry or hot stage microscopy.

The present article presents, through a case study, the advantages of the Raman hyperspectral imaging in the characterization of such formulations. Indeed, Raman chemical imaging may fully characterize SEDDS with single equipment and operator in a non-destructive way allowing the follow-up of the formulation during stability studies. Raman imaging is therefore a tool of choice in the PAT framework since it increases the knowledge of the formulation and the process.

A quantitative multivariate method using Raman hyperspectral imaging to assay the API in the lipid based formulation has been developed and fully validated following the "total error" approach.

1. Introduction

Following the Biopharmaceutical Classification System (BCS), drugs may be characterized according to their membrane permeability and their aqueous solubility (Amidon et al., 1995). Even if the actual tendency is to produce biopharmaceutical active pharmaceutical ingredient (API), the huge majority of new chemical entities (NCE) are little molecules obtained by organic chemistry synthesis. This implies that most NCE show a poor water solubility (Li et al., 2009) and are classified as BCS class 2 (poor solubility and high permeability). However, the main problem with BCS class 2 drugs is that they exhibit relatively poor bioavailability.

Several strategies may be used to address this: particle size decrease, polymorphism, amorphous drugs, complexation (with cyclodextrins or surfactants), solid solutions and dispersion, soluble prodrugs and salts (Leuner and Dressman, 2000). Another approach is the use of Self-Emulsifying Drug Delivery System (SEDDS). These liquid or semi-solid formulations are encapsulated into hard or soft capsules and generate an emulsion in the gastrointestinal tract facilitating the absorption of the drug (Mullertz et al., 2010). There exist a large variety of excipients that can be used ranging from non-polar lipids to polar lipids. Pouton (2006) proposed a Lipid Formulation Classification System (LFCS) categorizing the lipid based formulations according to their composition. The LFCS classifies the lipid based formulations as Type I if it is composed exclusively of oils, Type II if it is a mix of oils and water-insoluble surfactants, Type IIIA are the formulations composed of mainly of oils and small proportion of water-soluble surfactant, Type IIIB are composed of a small proportion of oils and a majority of water-soluble surfactants and hydrophilic co-solvents and finally Type IV are composed of a mix of surfactants and

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http://dx.doi.org/10.1016/j.ijpharm.2015.02.052
0378-5173/

co-solvents. The studied formulation is categorized as type IV formulation. This type of formulation allows an increased API charge compared to Type I formulations and produces very fine dispersions in an aqueous medium (Mullertz et al., 2010).

The main parameters that influence the activity of such formulations are the solid-state and the particle size of the API. The solid-state is commonly characterized using differential scanning calorimetry (DSC) (Balakrishnan et al., 2009; Craig, 2006; Kang et al., 2012) or X-ray powder diffraction (XRPD) (Docoslis et al., 2007; Hu et al., 2012; Wei et al., 2012) or vibrational spectroscopy (Milović et al., 2012; Nazzal et al., 2002; Stillhart and Kuentz, 2012). However these techniques are costly and require a highly trained user (for XRPD) and are destructive (for DSC).

Particle size analysis of lipid based formulations is a hard task since particles are formed during the cooling of the melt API/excipients matrix. So, it must be performed on the semi-solid dosage form after manufacturing. Therefore some researchers rather analyze the particle size of the produced emulsion in an aqueous medium (Agarwal et al., 2009; Ali et al., 2008). However, this is not applicable as quality control of a commercial formulation. Microscopic analysis with scanning or transmission electronic microscopes (SEM or TEM) may also be used (Balakrishnan et al., 2009,b; Yi et al., 2008a,b; Zhang et al., 2012). But once again it is costly, require highly trained users and it can only be used to see very small surfaces making representativity of the sampling a very big issue. Optical hot stage microscopy (possibly with polarized light) may also be used if the particle size is large enough (Bikiaris et al., 2005; Sprunk et al., 2012). But this technique has many drawbacks such as temperature degradation, polymorphism conversion but most of all the melt down of the smallest particles in the matrix making only possible the observation of the biggest particles.

Another technique that can be used to characterize both polymorphic state and particle size of the API is the Raman hyperspectral imaging. This technique combines the information obtained by Raman spectroscopy with spatial information.

Three configurations of Raman hyperspectral imaging systems exist: point mapping, line scanning and global imaging. The point scanning mode is by far the most used configuration. It consists of recording a spectrum at a specific spatial location, then the sample moves, another spectrum is recorded at an adjacent location and so on until the whole mapping area is covered. The line scanning mode records the spectra of a complete line of the sampled area simultaneously which fastens the analysis. Finally, in the global imaging configuration, the whole sample is illuminated and the intensity of a fixed number of wavenumbers is recorded returning a complete image of the sample for each wavenumber. In this case, the spatial resolution is limited by the number of pixels of the detector (Sacré et al., 2014a). In the present study, each imaging system worked in the point mapping mode.

Raman spectroscopy allows to characterize the solid-state of pharmaceutical powders (Brittain, 2009; Simone et al., 2014 Simone et al., 2014) but also to obtain quantitative information of an API (Breitkreitz et al., 2013) and because of the low wavelength laser used (visible to NIR light), it may provide high resolution (~1 μm) images (Adar et al., 2006).

It is therefore possible with a single technique to obtain both solid-state, quantitative and particle size information of a sample. Raman hyperspectral imaging is surely the technique of choice for the characterization of solid dispersions and among them SEDDS.

In the present study, we developed and validated a quantitative method based on hyperspectral Raman imaging to quantify a BCS 2 API in a lipid based formulation. To the author's best knowledge, it is the first time that a hyperspectral imaging quantitative method has been fully validated using the "total error" approach.

Moreover, two formulations were produced, one with the API totally dissolved in the matrix and a second one with 70% of the API dissolved in the matrix and 30% added as bulk powder. The second formulation mimics a bad processed medicine and Raman hyperspectral imaging has been used to characterize both formulations.

2. Experimental

2.1. Samples

The studied formulation consists of a BCS 2 API dispersed in a lipid matrix at a concentration of 28% (w/w). The excipient part is composed of lauroyl macrogol-32 glycerides (>50%), hydroxypropyl cellulose, macrogol 20000, sodium starch glycolate and ascorbyl palmitate by order of importance. The API and excipients were kindly donated by Galephar M/F.

2.1.1. Validation

Calibration and validation samples were prepared at 50, 75, 100, 125 and 150% of the target API concentration. Only the ratio API/excipients was changed keeping the ratio between excipients constant. For each concentration level, three independent series were realized with three replicates per series.

The samples were prepared by dispersing the melt API in the melt excipients. Once dispersed, the mix is cooled to room temperature and three small cylindrical samples (1 cm of diameter and 0.5 cm high) are deposited on a microscope slide constituting a series. Samples were then milled with a Leica EM Rapid milling system equipped with a tungsten carbide miller (Leica Microsystems GmbH, Wetzlar, Germany) to prepare their surface for Raman imaging experiments. After the Raman imaging experiments, samples were assayed by HPLC.

2.1.2. Industrial samples

The validated quantitative method was applied on industrial samples. Three samples per batch and three different batches (517811J, 12F04, 11I19) were analyzed. The semi-solid samples were taken out of the hard capsules and a sagittal cut was performed before milling. Once mapped, samples were analyzed by HPLC.

2.1.3. Samples for the case study

Two preparations were compared and fully characterized using Raman imaging:

- Preparation 1:100% of the API has been dissolved in the melted excipients. This preparation corresponds to an industrial batch without manufacturing issue.
- Preparation 2:70% of the API has been dissolved in the melted excipients and the remaining 30% were added as crystalline bulk powder to the solidified cooled preparation. This preparation mimics an industrial batch that encountered issues during process.

2.2. Reference method

2.2.1. Chemicals

Methanol HPLC grade was purchased from J.T. Baker (Deventer, Netherlands). Water was purified by a Millipore system (18.2 MΩ/cm resistivity, Milli-Q) before filtration through a 0.22 μm Millipore Millipak® – 40 disposable filter units (MilliporeCorporation, USA).