Powder Technology 281 (2015) 49–56

Contents lists available at ScienceDirect

Powder Technology

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

Automatic monitoring and quantitative characterization of sedimentation dynamics for non-homogenous systems based on image profile analysis

Xiaolong Lu [a,b,1], Zuhua Liao [b,c,1], Xue Li [b], Manli Wang [b,e], Li Wu [b,f], Haiyan Li [b], Peter York [b,d], Xu Xu [a,*], Xianzhen Yin [b,d,**], Jiwen Zhang [a,b,**]

[a] School of Mechanical Engineering (X. Lu), School of Chemical and Environmental Engineering (X. Xu), Shanghai Institute of Technology, Shanghai 201418, China
[b] Center for Drug Delivery System, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[c] School of Pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China
[d] Institute of Pharmaceutical Innovation, University of Bradford, Bradford, West Yorkshire BD7 1DP, United Kingdom
[e] School of Pharmacy, Anhui University of Chinese Medicine, Hefei 230038, China
[f] Research Center for Drug Metabolism, Jilin University, 130012 Changchun, China

ARTICLE INFO

Article history:
Received 20 November 2014
Received in revised form 16 March 2015
Accepted 30 April 2015
Available online 9 May 2015

Keywords:
Non-homogeneous system
Derivative mutation algorithm
Automatic monitoring
Image processing
Sedimentation dynamics
Suspensions

ABSTRACT

Sedimentation of non-homogeneous systems is the typical phenomenon indicating the physical instability as a key measure to the quality control of the preparation products. Currently, the determination methods for the sedimentation of non-homogeneous preparations are based on manual measurement or semi-quantitative observation, lacking of either automation or quantitative dynamic analysis. The purpose of this research was to realize automatic and quantitative monitoring of the sedimentation dynamics for non-homogenous systems as suspension, emulsions at laboratory level. Non-contact measurement method has been established to determine the sedimentation behaviors in a standard quartz tube for sedimentation, with internal diameter and height 23 mm and 215 mm, respectively, with controlled temperature and light intensity. As high performance camera has been equipped, the sedimentation images with high spatial and temporal resolution could be acquired, which can continuously capture sedimentation images with the resolution of 2048 × 2048 pixel at a maximum rate of 60 slides/s. All the pictures were processed to extract the luminance matrix top-down along the fixed vertical midline of each picture, which implied sedimentation characteristics of the system at the moment the picture was taken. Combining all the luminance matrixes along vertical middle lines of the pictures, a time-luminance matrix profile was obtained. Digital image processing techniques were used to eliminate interference and establish a three-dimensional surface model of the sedimentation dynamics. Then, the derivative mutation algorithm has been developed for the intelligent identification of sedimentation interface with threshold optimization so as to quantitatively analyze the sedimentation dynamics with visualization. The sedimentation curve and sedimentation dynamic equation of the non-homogeneous system were finally outputted by numerical fitting. The methodology was validated for great significance in determinations of small volume samples, parallel control multiple batches, and long period of time automatic measurement.

1. Introduction

Sedimentation [1–3] is the directional movement of particles under force fields due to the different densities between a dispersed phase and the liquid dispersion medium. Sedimentation of suspended material caused by gravity is defined as gravitational sedimentation, while sedimentation of suspended material resulting from centrifugal force is defined as centrifugal sedimentation.

The settling velocity of particles is influenced by the size [4,5] and density of particle, fluid density and viscosity, temperature, fluid motion, dispersion, agglomeration and other factors, with the settling velocity of particles in a viscous system lower than that in less viscous systems having the same fluid density [6]. The dominating factor controlling the settling velocity is particle size. The larger the particle size is, the smaller an influence of sedimentation trajectories under the thermal motion of the liquid molecules can have. When the diameter is

* Correspondence to: X. Xu, School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, China. Tel.: +86 21 60873235.
** Corresponding authors at: Center for Drug Delivery System, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China. Tel./fax: +86 21 20231980.
E-mail addresses: xuxu3426@sina.com (X. Xu), yinxianzhen0001@163.com (X. Yin), jwzhang@simm.ac.cn (J. Zhang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.powtec.2015.04.080
0032-5910/

smaller than 1–10 nm, the thermal motion of the molecules cannot be ignored, which has a greater impact on the sedimentation of particles. The measurement and evaluation of sedimentation are of importance in the pharmaceutical [7], food [8,9], and materials sectors [10] as well as other fields.

1.1. Importance of studying sedimentation behaviors

Non-homogeneous solid or liquid pharmaceutical preparations are in the form of molecular aggregates, particles or droplets dispersed in a medium, such as suspensions and emulsions are thermodynamically unstable systems, as particles are prone to settling/floating in density difference between solid and liquid. And physical stability is one of the critical aspects in ensuring safety and efficacy of drug products, and the sedimentation behavior of non-homogeneous preparations may be required to be adjusted to ensure desirable stability and quality of the product. Therefore, close attention should be paid to all the steps involved in product design, development, testing, processing and production.

The sedimentation rate is described by Stokes' law [11,12] which defines the important role of particle size, medium viscosity and density difference between medium and dispersed phase in determining the sedimentation rate. Decreasing size is the most common strategy used to reduce particle settling. Matching drug particle density with medium or increasing medium viscosity is the other widely used approaches to alleviate sedimentation problems. Thus evaluation of the sedimentation dynamics is important when attempting to improve the physical stability of non-homogeneous systems.

1.2. Methods for measurement of sedimentation

Currently, there are two main approaches to measure sedimentation of heterogeneous systems in the field of pharmacy: one is direct observation by the naked eye [13–16], the other one is to use instrument analysis, such as a particle size analyzer [17–19]. The sedimentation of non-homogeneous pharmaceutical systems is usually examined by transferring the suspensions into a stoppered measuring cylinder, storing undisturbed at room temperature and measure the sedimentation volume after a period of time. The sedimentation volume ratio (E_r), used as the primary parameter for the stability assessment, is calculated as:

$$E_r = \frac{H_c}{H_e} \times 100\% \tag{1}$$

where H_c is the height of the supernatant and H_e is the height of the total non-homogenous preparation. The sedimentation curve can be obtained by plotting the sedimentation volume ratio versus sedimentation time. For the sedimentation test based on Eq. (1), the Chinese Pharmacopeia defines the test as: After shaking suspensions for standing 3 h, then calculates the final height of suspended material sedimentation volume ratio. Therefore, the measurement results are relatively coarse.

For the test of the sedimentation kinetics, the traditional way of measuring sedimentation is tedious. Uncontrolled errors are introduced, when the values are read by eye. A computer based automatic method to monitor sedimentation is preferred to give accurate determinations. There are few reports on automatic monitoring for the sedimentation of non-homogeneous liquid systems, although a number of publications present accounts of conventional measurement by sludge settling [20–24] and liquid level detection [25–30]. Sensor based methods as optical and ultrasonic methods for automatic sedimentation analysis have been reported. The sedimentation of particles will cause changes in liquid pressure during the sedimentation process. A pressure sensor was installed in a sedimentation device to measure hydrostatic pressure at a certain distance from the bottom of the container. The output signal was fed to a recorder and software was used to calculate the settling velocity [31]. This method has advantages for large volume suspension systems, but the accuracy is limited. Three optical techniques were used and compared to study sedimentation behaviors of suspensions [32–34], monochromatic laser light sources were used to achieve the spatial light (angle) distribution of diffraction and scattering relevant to particle size distribution, average particle diameter and particle volume fraction. There was difference between the working principle of a Turbiscan optical analyzer and the experimental method of the present paper. In data processing, single spectra acquired at different time points were analyzed to determine the settlement interface by a Turbiscan optical analyzer. The environment conditions like the temperature may change during the acquisition process. Ultrasonic methods are nondestructive tools for characterizing emulsions and suspensions [35,36] and can be used to measure the particle size, disperse phase volume fraction, phase inversions, and creaming/sedimentation profiles. The limitation of the technique relates primarily to the ultrasonic wave frequency used.

In summary, the current automatic devices are restricted by their own measurement accuracy, environment and applicability. In an attempt to provide an alternative technique in this report, a non-contact continuous measurement method using visible light was established to acquire real time sample images automatically during the sedimentation process and establish a three-dimensional surface model of the sedimentation dynamics. The sedimentation interface was then identified based upon a derivative mutation algorithm with threshold optimization. Thus, the sedimentation curve and sedimentation dynamic equation of the non-homogeneous system were derived by numerical fitting.

2. Materials and methods

2.1. Theory

When light from one medium (of refractive index n_1) transmits into another medium (of refractive index n_2), reflection and refraction may occur at the same time at the junction of the two media (often referred to as interface). The reflectivity of different types of materials and different wavelengths of light source is different. The refractive index of the different objects can be distinguished by the intensity of reflected light [37,38].

When light (I_0) irradiated onto an absorbing medium surface, after passing through a certain thickness of the media, the medium absorbs a part of light energy (I_a), so the strength of the transmitted light will be weakened [39,40]. The wavelength range of visible light is 770 to 350 nm, the particle size of the solid particles in the solution is in the micron level, so the scattering intensity (I_s) and I_a is difficult to be measured.

$$I_0 = I_r + I_t + I_a + I_s \tag{2}$$

where I_0, I_t, I_r, I_a, and I_s are the intensity (power per unit area) of the incident radiation, the transmitted radiation, the reflected radiation, the absorption radiation and the scattering radiation, respectively.

$$I_r = I_{r1} + I_{r2} \tag{3}$$

$$I_t = I_{t1} + I_{t2} \tag{4}$$

where I_{r1} and I_{t1} are the intensity of the reflected radiation and the transmitted radiation of the dilute phase, I_{r2} and I_{t2} are the intensity of the reflected radiation and the transmitted radiation of the concentrated phase. The value of I_r is mainly dependent on the reflection coefficient of the object. However, the reflection coefficient of the solid particles or liquid droplets is much larger than the solution in the non-homogeneous system.