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ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 1159–1162
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Rapid method to study the sedimentation of a pigment suspension prepared for coating fluids

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Received 18 December 2006; received in revised form 1 March 2007; accepted 4 April 2007
Available online 8 April 2007

Abstract

Film coating fluids commonly contain a pigment suspension. The sedimentation of insoluble particles in the coating suspension is one of the main problems during the formulation of the coating fluid. The aims of this work were to investigate the suitability of an energy-dispersive X-ray fluorescence analyser for rapid measurement of the sedimentation of titanium dioxide in aqueous suspensions. The suspensions were produced with a high-speed Ultra-Turrax. The process factors evaluated were the stirring rate, time and volume, and the process of sedimentation of the pigment. The enrichment of the pigment at the bottom of the sample holder was followed by means of the very rapid method of energy-dispersive X-ray fluorescence analysis. It can be concluded that the sedimentation of the particles is described by the Weibull equation. With an appropriate combination of the factors, a threefold increase in the sedimentation time was achieved. The mathematically based information (sedimentation time, kinetics of sedimentation, etc.) is essential for an exact evaluation of the preparation of the coating fluid. The understanding of the process through use of this test method leads to the ability to identify the critical control points of film coating.

Keywords: Energy-dispersive X-ray fluorescence analysis; Factorial design; High-shear mixer; Pigment suspension; Sedimentation; Titanium dioxide

1. Introduction

Film-forming polymers in aqueous dispersions are increasingly used during the production of coated solid dosage forms [1]. Various types of polymers can be used to form aqueous dispersions, and numerous water-soluble and insoluble additives are applied to change the properties of the films and to increase the processibility of these liquids [2,3]. Insoluble pigments (e.g. iron oxide, titanium dioxide, etc.) are applied to ensure the appropriate appearance of the coated product [4]. They can modify the properties of the film formed [5,6] and thus their homogeneous distribution is indispensable.

The suggested mixing sequence for the preparation of a coating liquid containing insoluble particles is very important. According to a manufacturer of dispersions, the first step is the preparation of the pigment suspension [7]. In this case, the intensive homogenization of the materials (glidants, pigments, plasticizers and other excipients) in water must be performed with a high-speed mixing apparatus. After this, the freshly prepared homogeneous pigment suspension must be gently mixed with the polymer dispersion. High-speed mixing can cause precipitation of the polymers and foaming, and this apparatus can therefore not be used in this step [8,9]. The even distribution of the insoluble particles in the pigment suspension is very important because gentle mixing cannot break pigment aggregates.

The main problem that can arise during formulation of the coating fluid is the sedimentation of the pigments, which can cause an uneven coating layer and/or difficulties in the coating process. Various additives are applied to eliminate this problem for orally or topically used suspensions [10]. These materials are not recommended for pigment suspensions prepared for coating dispersions because of the possibility of changes in the properties of the films.

Despite the importance of sedimentation as a critical control point in the formulation of the coated product, this has been relatively neglected to date. The difficulty in the rapid determination of the homogeneity of the pigment is its sedimentation during the sampling. The main objective of our project was to establish an exact quick method with which to evaluate the sedimentation of pigment suspensions. The aims of this work were

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doi:10.1016/j.jpba.2007.04.003

to investigate the suitability of an energy-dispersive X-ray fluorescence analyser for rapid measurement of the sedimentation of pigments and to determine the parameters that can be applied for the preparation of pigment suspensions. The technique is suitable for direct measurement of the element component of a drug [11].

When a material is irradiated by the beam from an X-ray tube, its constituent atoms are excited. This causes them to emit X-rays as fluorescence. Each element in the sample emits its own uniquely characteristic fluorescent radiation, with an intensity directly related to the concentration of that element in the material. This phenomenon is the basis of X-ray fluorescence spectrometry.

Titanium dioxide was applied as an insoluble additive in our study. For an appropriate light protective effect, the even distribution of these particles is necessary [12]. An Ultra-Turrax mixer was used to disperse the powder in water. In consequence of their unwanted effects (modification of the permeability, solubility and stability [13–15]), other additives (suspending and viscosity-increasing agents), were not used. The titanium content of the pigment suspension and the enrichment of the pigment at the bottom of the sample holder were measured with an energy-dispersive X-ray fluorescence analyser. The kinetics of sedimentation of the pigment suspension was followed. Several technological aspects were evaluated with the aim of decreasing the sedimentation. The mathematically determined effects of different factors were compared by means of a factorial design. This information is very useful for the application of process analytical technology (PAT). Since gaining a deep understanding of the manufacturing process is at the heart of PAT [16–18].

2. Experimental

2.1. Materials

Commercial titanium dioxide (Merck GmbH, Darmstadt, Germany) was used, where the particles form aggregates. It was dispersed in distilled water at a concentration of 10%.

2.2. Factorial design

The fluid was stirred in glass beakers with identical dimensions (7.7 cm in diameter) with an Ultra-Turrax mixer (IKA Ultra-Turrax T25 basic, IKA-Werke GmbH & Co. Kg, Staufen, Germany). The diameter of the turbine was 1.85 cm in diameter. The turbine of mixer was located in the midst of container. A 2^3 full factorial design was applied for different mixings; the factors were the stirring rate (X_1), the stirring time (X_2) and the volume (X_3), with the levels to be seen in Table 1. The eight experimental set-ups were supplemented with a central point.

Table 1
Levels of factors

Factor	Low (−)	Zero (0)	High (+)
X_1	9500 rpm	13500 rpm	17500 rpm
X_2	5 min	7.5 min	10 min
X_3	100 ml	150 ml	200 ml

Statistica for Windows 6.1 AGA (StatSoft, Inc. Tulsa, USA) software was applied to determine the effects of the factors. The following linear approach was applied to determine the surface of the response:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

The b_0 (intercept) is the mean for y value of nine samples.

2.3. Determination of titanium dioxide content

The titanium contents of the pigment suspensions and the enrichment of the pigment at the bottom of the sample holder were measured with an energy-dispersive X-ray fluorescence analyser (PW 4025/00, Minipal Philips, Almelo). This compact table-top instrument can be used to measure the elemental range from sodium (Na) to uranium (U), in the concentration range from ppm to 100%, and it ensures very rapid and facile data acquisition.

The conditions applied during the measurements were 8 kV, 120 μA and an air purge with a kapton filter. The samples were measured for 20 s. The linearity of calibration was checked between the titanium content of 4–12% (6.6–20% of titanium dioxide). The R^2 was 0.9827. The accuracy of the method was checked with liquids containing a certain amount of titanium dioxide. The difference between calculated and measured concentration was not significant (t-test, $p < 0.05$). The pigment suspensions poured into the sample holder and they were tested directly without withdrawing. Three parallel tests were performed.

The sedimentation curves were constructed from the measured data. The maximum in the sedimentations when the concentration reached the highest level, was taken as 100%. The other results were calculated from the concentration ratios. The fitting revealed that these curves can be described by the Weibull model [19]. A non-linear fitting approach with the following equation was applied:

$$M = M_0 \left\{ 1 - \exp\left[-\frac{(t-T)^\beta}{a} \right] \right\}$$

where M is the percentage sedimentation up to time t, M_0 the maximum percentage sedimentation, T the delay time, β the shape parameter, and a is the scale parameter.

The characteristic sedimentation time ($t_{63.2\%}$), i.e. the time necessary to reach 63.2% of the maximum enrichment of titanium dioxide, was determined from the curve.

3. Results and discussion

The enrichment of titanium dioxide at the bottom of the sample holder was readily measured with this very rapid test method. It can be seen from the sedimentation profile that there were no

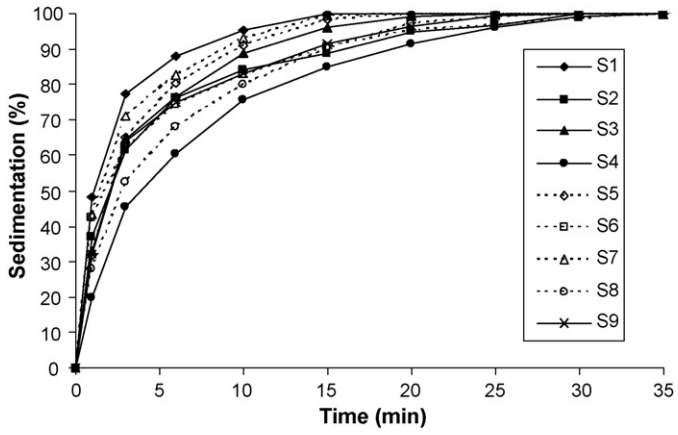

Fig. 1. Sedimentation curves for pigment suspensions.

fundamental differences between the characteristics of the sedimentation curves, but the courses were not identical, e.g. the maximum sedimentation was reached at 15 min for S1 and at 35 min for S4 (Fig. 1).

The fittings were very good, because the R^2 values were higher than 0.99. The results derived from the fitting were different for the different samples (Table 2). Since the characteristic sedimentation time of the sample with a low mixing rate and a low mixing time was very short, the addition of this suspension to the polymer dispersion must be very quick. Accordingly, increase of this time is inevitable. An appropriate combination of the factors can cause a threefold increase in the sedimentation time (see Section 3 for S1 and S4). The values of the shape parameters (β) are less than 1, and thus the curves are saturation curves with a fast initial increase.

The values of the scale parameter (a) indicate the speed of increasing of the curve. The higher the value is, the slower the sedimentation is. The highest one was detected for S4 (just as it was seen at the sedimentation time).

The characteristic sedimentation times were compared by means of the factorial design. The linear estimation with the interactions was very good ($R = 0.9998$). Table 3 presents the ranked order of the factors. The stirring rate, the time and the interaction of these factors were significant in the 99% confidence interval. The higher are the values of these factors, the longer is the sedimentation time. Change of the stirring rate can cause a more than twofold increase in the sedimentation time relative to the increase caused by change of the stirring time. The sample volume on this laboratory scale was not a significant factor, but it can be concluded that increase of the volume decreases the sedimentation time. This statement is indicated by the negative sign of the coefficients for volume and the two-factor interaction containing the mixing volume.

The three-factor interaction was less relevant. The positive sign in the equation of the response surface indicates a slight increase in the sedimentation time.

Table 2
Kinetic study parameters

Sample	X_1	X_2	X_3	$t_{63.2\%}$ (s)	Corr.	a	β
S1	−	−	−	2.03	0.9968	1.74	0.9613
S2	+	−	−	4.28	0.9957	3.79	0.9068
S3	−	+	−	2.90	0.9969	2.75	0.9289
S4	+	+	−	6.69	0.9955	4.42	0.8975
S5	−	−	+	2.89	0.9967	2.45	0.9398
S6	+	−	+	4.29	0.9952	3.61	0.9014
S7	−	+	+	2.42	0.9972	2.13	0.9468
S8	+	+	+	6.03	0.9955	3.94	0.9102
S9	0	0	0	3.92	0.9971	3.38	0.9130

Table 3
Factorial design parameters

Factors	Coefficients
b_0	3.9388*
b_1	1.3813*
b_2	0.5688*
b_{12}	0.4687*
b_{23}	−0.2513
b_{13}	−0.1288
b_{123}	0.0837
b_3	−0.0338

* Significant ($p < 0.01$).

4. Conclusions

It may be concluded that the change in the concentration of titanium dioxide can be detected by energy-dispersive X-ray fluorescence analysis. In a pigment suspension without additives, the sedimentation is a very quick process, which can be described by the Weibull model. The sedimentation of this pigment suspension can be changed via the appropriate parameters of the Ultra-Turrax mixer. The application of this rapid test method and the determination of the characteristic sedimentation time allowed comparison of the effects of different technological parameters.

This information is indispensable for a more accurate knowledge of the preparation of the coating fluid and for detection of the critical control point of coating. Accordingly, their precise control can promote the formulation of a coating fluid and the occurrence of the coating process with less chance of disturbing effects.

Acknowledgement

This work was supported by Hungarian Scientific Research Fund (OTKA) grant F-049310.

References

[1] G. Cole, J. Hogan, M. Aulton, Pharmaceutical Coating Technology, Taylor & Francis Ltd., London, 1995.
[2] K.H. Bauer, K. Lehmann, H.P. Osterwald, G. Rothang, Coated Pharmaceutical Dosage Forms, Medpharm GmbH Scintific Publishers, Stuttgart, 1988.
[3] S. Nimkulrat, K. Suchiva, P. Phinyocheep, S. Puttipipatkhachorn, Int. J. Pharm. 287 (2004) 27–37.
[4] A.P. Plumb, R.C. Rowe, P. York, C. Dohery, Eur. J. Pharm. Sci. 16 (2002) 281–288.
[5] H.U. Petereit, W. Weisbrod, Eur. J. Pharm. Biopharm. 47 (1999) 15–25.

[6] L.A. Felton, J.W. McGinity, Drug. Dev. Ind. Pharm. 28 (2002) 225–243.
[7] Eudragit® brochure Röhm GmbH & Co. KG, Pharma Polymers, Darmstadt, 2005.
[8] K. Lehmann, Practical Course in Film Coating of Pharmaceutical Dosage Forms with Eudragit®. Pharma Polymers, Darmstadt, 1999.
[9] M.E. Aulton, Pharmaceutics The Science of Dosage Form Design, Churchill Ltd., Livingstone, 2002.
[10] R.C. Rowe, P.J. Sheskey, P.I. Weller, Handbook of Pharmaceutical Excipients, 4th ed., Pharmaceutical Press, London, 2003.
[11] L. Reimer, Scanning Electron Microscopy, Physics of Image Formation and Microanalysis, Springer–Verlag, Heidelberg, 1985.
[12] W. Weibull, J. Appl. Mech. 18 (1951) 293–297.
[13] J. Bajdik, K. Pintye-Hódi, G. Regdon Jr., P. Fazekas, P. Szabó-Révész, I. Erős, J. Therm. Anal. Cal. 73 (2003) 607–613.
[14] F. Lecomte, J. Siepmann, M. Walther, R.J. MacRae, R. Bodmeier, J. Control. Release 99 (2004) 1–13.
[15] M.A. Frohoff-Hülsmann, A. Schmitz, B.C. Lippold, Int. J. Pharm. 177 (1999) 69–82.
[16] J. Bajdik, G. Regdon Jr., G. Lebák, O. Berkesi, K. Pintye-Hódi, Polym. Adv. Technol. 17 (2006) 814–817.
[17] B. Davies, S. Ellis, Pharm. Techn. Europe 17 (8) (2005) 17–23.
[18] T. Kourti, Anal. Bioanal. Chem. 384 (2006) 1043–1048.
[19] I. Paris, A. Janoly-Dumenil, A. Paci, L. Mercier, P. Bourget, F. Brion, P. Chaminade, A. Rieutord, J. Pharmaceut. Biomed. Anal. 41 (2006) 1171–1178.