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Setting the process parameters for the coating process in order to assure tablet appearance based on multivariate analysis of prior data

Shuichi Tanabe[a,b,*], Hiroshi Nakagawa[a], Tomoyuki Watanabe[a], Hidemi Minami[a], Manabu Kano[c], Nora A. Urbanetz[b]

[a] Formulation Technology Research Laboratories, Daiichi Sankyo Co., Ltd., Hiratsuka 254-0014, Japan
[b] Pharmaceutical Development, Daiichi Sankyo Europe GmbH, Pfaffenhofen 85274, Germany
[c] Department of Systems Science, Kyoto University, Kyoto 606-8501, Japan

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ABSTRACT

Designing efficient, robust process parameters in drug product manufacturing is important to assure a drug's critical quality attributes. In this research, an efficient, novel procedure for a coating process parameter setting was developed, which establishes a prediction model for setting suitable input process parameters by utilizing prior manufacturing knowledge for partial least squares regression (PLSR). In the proposed procedure, target values or ranges of the output parameters are first determined, including tablet moisture content, spray mist condition, and mechanical stress on tablets. Following the preparation of predictive models relating input process parameters to corresponding output parameters, optimal input process parameters are determined using these models so that the output parameters hold within the target ranges. In predicting the exhaust air temperature output parameter, which reflects the tablets' moisture content, PLSR was employed based on prior measured data (such as batch records of other products rather than design of experiments), leading to minimal new experiments. The PLSR model was revealed to be more accurate at predicting the exhaust air temperature than a conventional semi-empirical thermodynamic model. A commercial scale verification demonstrated that the proposed process parameter setting procedure enabled assurance of the quality of tablet appearance without any trial-and-error experiments.

1. Introduction

The utilization of a tablet film coating process is recognized as one of the common unit operations in the pharmaceutical industry. In general, the film coating on pharmaceutical solid dosage forms aims at providing distinguishability, functionality, and elegance (Knop and Kleinebudde, 2013; Teckoe et al., 2013). Suitable process conditions that assure a desired product quality often depend on manufacturing scale, equipment used, and formulation, and thus process parameter settings have generally been researched at each scale in most current equipment and drug product formulations. Considering the concept of quality by design (QbD), a systematic approach defined in ICH Q8 should be applied for determining manufacturing process parameter settings to assure the desired product quality (ICH, 2009). An enhanced approach for determining the functional relationships between process parameters and critical quality attributes (CQAs), such as tablet functionality and appearance, has been developed to realize more robust processes and higher assurances of the CQAs (Rajalahti and Kvalheim, 2011; Zacour et al., 2012). Teckoe et al. (2013) developed a design space through design of experiments (DoE) to visualize acceptable ranges of process parameters that can assure two CQAs, i.e., tablet appearance and disintegration time, within an acceptable process time. DoE is a typical approach for developing a reliable process model with minimal and well-organized experiments. As resources are limited and as the coating process is typically the final process of a tablet's manufacturing, it has been considered practically difficult to conduct many commercial scale experimental studies, even with the benefit of sophisticated DoEs to reduce the amount of experimentation and its impact on pharmaceutical companies. A significant workload reduction could be attained if prior knowledge (such as existing product batch records) is fully utilized for product-independent process modeling and optimization. The product-independent process models for assuring the CQA of tablet appearance require standardized

* Corresponding author at: Daiichi Sankyo Europe GmbH, Pharmaceutical Development, Luitpoldstrasse 1, Pfaffenhofen 85276, Germany.
E-mail address: tanabe.shuichi.h3@daiichisankyo.co.jp (S. Tanabe).

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product-independent output parameters. Macroscopic and microscopic moisture content, spray mist condition, and mechanical stress on tablets are the typical product-independent output parameters that affect tablet appearance (Levin, 2001), and the desired appearance can be attained by setting these four output parameters within their respective optimal ranges (Pandey et al., 2006).

Regarding macroscopic and microscopic moisture content, exhaust air temperature T_{EA} and local moisture M_{LM}, defined as the maximum amount of water received in a single rotation, have been reported as macroscopic and microscopic indices, respectively, to derive desirable process parameters with less trial-and-error experiments (Pandey et al., 2006; am Ende and Berchielli, 2005; Prpich et al., 2010). Few models for the mist condition have been reported, i.e., size and distribution of mist droplets in the spray area, because this mist condition can be easily evaluated through an actual experiment without coating. Mechanical stress, which is the last parameter in the four output parameters affecting coating appearance, is difficult to measure directly; therefore, some computational simulation models for predicting the mechanical stress on tablets have been developed based on a discrete element method (Hancock et al., 2010; Kodam et al., 2012). However, from a viewpoint of practicality, it would not always be suitable for predicting the optimal coating parameter because of the huge workload involved in generating the simulation and the difficulty in validating the predicted mechanical stress on tablets. In this report, hence we focused on optimizing the former two parameters of macroscopic and microscopic moisture content by using prediction models, and the latter two of mist condition and mechanical stress were determined based on the results of previous experience.

There is a traditional chemical engineering calculation used to justify the relationship between moisture content and temperature, however, the conventional model for predicting exhaust air temperature T_{EA} exhibits a challenge in its prediction accuracy. T_{EA} has been predicted by semi-empirical thermodynamic models (am

Table 1
Calibration set consisting of 50 samples.

No.	Formulation	T_D °C	H_{IA} g water/kg DA	T_R °C	T_{IA} °C	F_{IA} m^3/min	D rpm	M_W g/min	W_T kg	T_{EA} °C
1	A	20.9	9.488	22.8	70	40	2.0	268.7	162.92	48.6
2	A	20.8	9.252	22.8	70	40	3.0	275.9	162.92	48.9
3	A	21.0	9.360	22.8	70	40	6.0	386.6	162.92	45.1
4	A	24.9	7.797	22.6	70	40	6.0	384.8	187.52	44.4
5	A	26.2	4.686	22.0	70	40	6.0	384.4	190.14	44.7
6	A	25.0	6.457	22.5	70	40	2.0	275.3	191.49	47.5
7	A	25.3	6.802	22.5	70	40	3.0	275.8	191.49	47.4
8	B	25.3	4.925	22.5	70	40	3.0	320.3	186.12	46.4
9	B	24.5	6.054	22.5	70	40	2.0	329.5	190.26	45.3
10	B	25.5	6.404	22.5	70	40	6.0	384.3	190.26	44.3
11	B	26.6	9.331	22.0	70	40	2.0	321.1	191.95	46.4
12	C	23.9	10.403	22.1	72	50	4.0	437.2	332.24	47.4
13	C	24.1	10.741	22.1	72	50	7.0	492.6	332.24	46.7
14	C	23.5	10.381	22.2	75	50	3.0	325.3	306.30	51.7
15	C	24.2	11.022	22.2	72	50	5.0	489.4	306.30	46.6
16	C	24.0	10.680	22.2	72	50	7.0	491.8	306.30	47.0
17	D	23.3	10.264	22.8	72	50	4.0	424.7	337.37	48.0
18	D	23.7	10.500	22.8	72	50	7.0	492.9	337.37	46.8
19	D	23.5	10.593	22.2	73	50	4.0	438.2	299.15	48.5
20	D	23.7	10.714	22.2	73	50	8.0	492.4	299.15	47.4
21	D	26.1	3.374	22.1	75	50	3.0	341.6	340.87	50.1
22	D	26.0	3.354	22.1	72	50	4.0	401.6	340.87	48.5
23	D	26.4	3.650	22.1	72	50	7.0	452.6	340.87	47.6
24	E	23.0	10.296	22.0	70	50	2.5	434.5	325.23	45.5
25	E	23.3	10.473	22.0	70	50	4.0	434.1	325.23	46.6
26	E	23.8	10.560	22.0	68	50	2.0	439.9	307.65	44.0
27	E	23.8	10.560	22.0	70	50	5.0	492.9	307.65	44.5
28	E	25.8	8.352	22.4	78	50	2.5	440.7	343.21	50.1
29	E	25.8	8.564	22.4	80	50	4.0	439.9	343.21	53.3
30	E	24.0	9.016	22.4	85	60	2.5	331.4	326.32	61.7
31	E	24.1	9.071	22.4	85	60	4.0	331.1	326.32	63.9
32	E	23.7	9.228	22.6	80	60	2.5	322.9	339.06	56.4
33	E	23.9	9.151	22.6	80	60	4.0	330.5	339.06	58.6
34	E	24.6	9.350	22.3	80	55	2.5	329.4	341.34	55.6
35	E	24.6	9.152	22.3	80	55	4.0	330.9	341.34	57.5
36	E	24.4	9.237	22.2	80	50	2.5	330.2	341.74	54.1
37	E	24.4	9.237	22.2	80	50	4.0	329.6	341.74	55.8
38	F	24.2	9.512	22.1	63	50	4.0	417.0	497.63	41.9
39	F	23.1	7.995	22.6	63	50	4.0	410.2	497.47	42.0
40	G	24.1	9.071	22.1	63	50	5.0	415.9	482.38	42.5
41	G	24.0	2.790	22.4	63	50	5.0	414.7	482.98	42.4
42	G	23.9	3.330	22.4	63	50	5.0	414.2	482.98	42.1
43	H	25.4	2.830	22.7	70	50	6.0	486.9	385.23	44.8
44	H	25.3	9.381	22.6	70	50	3.0	436.2	347.66	45.8
45	H	23.9	5.202	22.6	70	50	4.0	435.9	360.29	46.0
46	I	23.1	9.526	22.7	70	50	4.0	437.3	370.17	45.8
47	I	25.9	8.489	23.0	70	50	3.0	434.9	375.39	46.2
48	I	25.1	8.349	23.0	70	50	6.0	488.4	375.39	44.9
49	J	23.8	10.775	22.2	73	50	3.0	429.9	307.35	48.4
50	J	23.7	10.714	22.2	72	50	2.0	494.9	307.35	46.2