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RESEARCH ARTICLE

Modeling of latent structure of indomethacin solid dispersion tablet using Bayesian networks

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Abstract

Background: When designing pharmaceutical products, the relationships between causal factors and pharmaceutical responses are intricate. A Bayesian network (BN) was used to clarify the latent structure underlying the causal factors and pharmaceutical responses of a tablet containing solid dispersion (SD) of indomethacin (IMC).

Method: IMC, a poorly water-soluble drug, was tested with polyvinylpyrrolidone as the carrier polymer. Tablets containing a SD or a physical mixture of IMC, different quantities of magnesium stearate, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose, and subjected to different compression force were selected as the causal factors. The pharmaceutical responses were the dissolution properties and tensile strength before and after the accelerated test and a similarity factor, which was used as an index of the storage stability.

Result: BN models were constructed based on three measurement criteria for the appropriateness of the graph structure. Of these, the BN model based on Akaike's information criterion was similar to the results for the analysis of variance. To quantitatively estimate the causal relationships underlying the latent structure in this system, conditional probability distributions were inferred from the BN model. The responses were accurately predicted using the BN model, as reflected in the high correlation coefficients in a leave-one-out cross-validation procedure.

Conclusion: The BN technique provides a better understanding of the latent structure underlying causal factors and responses.

Keywords: Bayesian network, simulations, solid dispersion, solid dosage form, physical characterization, formulation

Introduction

The solid dispersion (SD) system is one of the methods used to enhance the dissolution rates of drugs with limited water solubility in inert carriers. Many studies of SD carriers have been reported[1]. Polyvinylpyrrolidone (PVP) is recognized as a superior polymer for use as an SD carrier[2–5]. However, there are several disadvantages of the SD method, including manufacturing difficulties, i.e. the SD powders are generally soft and tacky with poor flowability and compressibility[6]. Therefore, the SD is rather difficult to handle when a tablet is chosen as the final product formulation.

When designing pharmaceutical products, the relationships between causal factors and pharmaceutical responses are intricate. Therefore, the formulators' expertise and experience are essential in designing an acceptable product formulation. The empirical approach requires a prolonged development time and significant resources. In recent years, regulatory authorities such as the US Food and Drug Administration[7] and the International Conference on Harmonisation (ICH) have promoted and requested the application of quality-by-design principles to facilitate the exchange of complex information about chromatographic selectivity and critical resolution values to support better method control, including method transfer[8]. In particular, according to the ICH Q8 guidelines, a scientific understanding of the formulation and manufacturing method is required[9]. To gain insight into pharmaceutical formulations, a quantitative visualization technique is needed to clarify the relationships between the causal factors and the pharmaceutical

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responses. However, it can be difficult to achieve an overall view of the multivariate data obtained.

A Bayesian network (BN) is potentially useful in formulation development. BN is a directed acyclic graphical approach that expresses the probabilistic causal relationships among attributes, in which probabilistic relationships are expressed by nodes and the links connecting the nodes[10]. BN offers many advantages over a sample of all possible observations. Recently, BN has been used widely in various fields, including applied statistics, medicine, and bioinformatics[11–14].

The purpose of this study was to clarify the latent structure underlying the causal factors and pharmaceutical responses involved in preparing indomethacin (IMC) SD tablets with high hardness and high storage stability.

Materials and methods

Materials

IMC, a model poorly water-soluble drug, and magnesium stearate (Mg-St) were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan). PVP K30 was purchased from Sigma-Aldrich Co., Ltd (St Louis, MO, USA). Microcrystalline cellulose (MCC; Ceolus PH-101, Asahi Kasei Chemicals Co., Ltd, Tokyo, Japan), lactose (LAC; 200-mesh grade, DMV International, Veghel, the Netherlands), low-substituted hydroxypropyl cellulose (L-HPC; LH-21, Shinetsu Chemical Co., Tokyo, Japan), and corn starch (CS; Nihon Shokuhin Kako Co., Ltd, Tokyo, Japan) were gifts from Daiichi Sankyo Co., Ltd (Tokyo, Japan).

Preparation of SDs and physical mixtures

An IMC/PVP SD was prepared using the solvent evaporation technique. Equal parts of IMC and PVP were dissolved in 95% (v/v) ethanol at 60°C to produce a clear solution. The solvent was then removed at reduced pressure (14 mmHg) at 60°C, using a rotary evaporator. The final residue was maintained at reduced pressure for 24 h to completely eliminate the solvent. It was then milled and the particles passed through a 250-μm sieve. These were then stored in a desiccator over silica gel to prevent their absorption of humidity. This sample was analyzed by differential scanning calorimetry (DSC; Thermo plus DSC 8230, Rigaku, Tokyo, Japan) and a powder X-ray diffractometer (XRD; RINT-2000 X-ray diffractometer, Rigaku, Tokyo, Japan), and the amorphous state of the IMC was confirmed. A physical mixture (PM) was obtained by blending IMC and PVP in a polyethylene bag.

Experiment design

An L16 (2^5) fractional factorial experimental design was used to evaluate the relative contributions of the effects of the causal factors. The IMC tablets prepared as SD or PM (X_1), the quantities of Mg-St (X_2), MCC (X_3), and L-HPC (X_4), and the compression force (X_5) were selected as the causal factors. The 16 kinds of tablet formulations prepared are summarized in Table 1. The total mass of each tablet was adjusted to 200 mg using LAC and CS in a ratio of 7:3 (w/w).

Preparation of IMC tablets

All ingredients were dried at 75°C for 12 h. The ingredients were accurately weighed according to the experimental formulations, and all the ingredients were blended in a polyethylene bag for 2 min. The final blend was directly compressed into round-faced tablets (200 mg, 8 mm diameter) with a tableting machine (HANDTAB-100, Ichihachi-Seiki Co., Ltd, Kyoto, Japan).

Dissolution test

The dissolution test was performed with a JP XV dissolution test apparatus (paddle method) using 900 mL purified water at 37°C with stirring at 50 rpm. The samples were withdrawn and filtered after 5, 10, 15, 20, 30, 40, 50, and 60 min. The IMC concentration in the medium was measured spectrophotometrically at 320 nm with a Jasco Ubest-30 spectrophotometer (Japan Spectroscopic Co. Ltd, Tokyo, Japan). The dissolution rates of the IMC tablets at 10 min (D_{10}) and at 60 min (D_{60}), measured before and after the accelerated test, were selected as the pharmaceutical responses. The dissolution rates of three tablets of each formulation were measured.

Hardness test

The hardness of the tablet was determined with the Tablet Hardness Tester (Ogawa Seiki Co., Tokyo, Japan). Tensile strength (TS) was calculated as:

$$\mathrm{TS} = \frac{2F}{\pi dt} \tag{1}$$

where F is the maximal diametrical crushing force, and d and t are the diameter and thickness of the tablet, respectively. The TSs of three tablets of each formulation were measured.

Accelerated test

To evaluate the effects of stress conditions on the dissolution profiles and TS, the accelerated test was performed by storing the tablets at 40°C and 75% relative humidity for 2 weeks in a stability chamber (CSH-110; ESPEC Co., Osaka, Japan). The samples were then stored in a desiccator over silica gel at room temperature.

Evaluating the storage stability of IMC tablets

The similarity factor (f_2) was used to evaluate the similarity of the dissolution profiles before and after the accelerated test. f_2 is a measure of the similarity in the percentage dissolution between two curves[15]. In this study, f_2 was used as the criterion of storage stability of the dissolution profiles from 5 to 60 min.

Analysis of variance

To evaluate the significance of the effect of causal factors and their interactions, the data obtained from the

experimental design were analyzed by analysis of variance (ANOVA). The revised sum of squares (S′) obtained by subtracting the mean square of the error term from the mean square of each factor was used to estimate the contribution ratio. Contribution ratios of less than 5% were pooled as the error term.

BN model construction

The BayoNet System software, version 4.0.2 (Mathematical Systems Inc., Tokyo, Japan) was used to determine the BN structure. As measures of appropriateness, Akaike's information criterion (AIC), minimum description length (MDL), and maximum log likelihood (ML) were used. To construct the BN, candidates for the parent node (explanatory variable) were required. In this study, the factors were assigned as the candidates, and the responses of the tablets (D_{10}, D_{60}, and TS) were assigned as the child nodes (dependent variables). The responses of the tablets were discretized into three categories (low, medium, and high) using the K-means method on the BayoNet system.

Results

Responses before and after the accelerated test

Figure 1 shows the dissolution profiles for IMC from formulations Rp.2, Rp.7, Rp.11, and Rp.13, shown as typical examples. Before the accelerated test, the D_{60} values for the SD tablets were higher than those for the PM tablets, as summarized in Table 1. After the accelerated test, the initial dissolution rate was increased in the SD tablets, although that of the PM tablets had hardly changed. When analyzed by DSC and XRD, no recrystallization of IMC was seen in the SD tablets after the accelerated test (data not shown). Table 1 also shows the TS values for the test formulations before the accelerated test. The TS values for the PM tablets improved after the accelerated test, although those of the SD tablets were hardly changed (data not shown).

To clarify the causal relationships between the formulation factors and the pharmaceutical responses, ANOVA was applied before the BN analysis. The causal factors X_1 and X_5 and the two interactions $X_1 \times X_5$ and $X_4 \times X_5$ significantly affected D_{10}, and the contributions of X_1 and X_5, in particular, were extremely high compared with those of the other factors. The contribution ratios for D_{60} indicated that more than 80% of the variance was attributable to X_1. Furthermore, X_2 strongly affected the TS values, and X_1 significantly affected the f_2 factor.

Visualization of the latent structure using BN

To visualize the latent structure between the causal factors and the responses, a BN method was applied to the data points. The optimal BN models were predicted using AIC, MDL, and ML as the judging standards (Figure 2). The numbers of links in the BN models based on AIC, MDL, and ML were 9, 5, and 16, respectively. The BN model with MDL was the simplest and the model with ML was the most complicated. The intermediate model was obtained with AIC. These BN models were compared with the results obtained with ANOVA. Because the model based on AIC was closest to the results of ANOVA, it is likely that the AIC model appropriately demonstrates the latent structure of the tablet formulation containing IMC SD. D_{10} was affected by X_1, X_4, and X_5, D_{60} was affected by X_1 and X_4, and TS was affected by X_1, X_2, and X_3. The factor f_2 correlated predominantly with X_1.

The responses were predicted using conditional probability distributions (CPDs). As shown in Figure 3a, the CPDs indicated whether SD or PM was crucial to the high or low values for D_{10}. The SD tablets produced with 15% L-HPC and 8 kN compression force resulted in the highest D_{10} value. In contrast, the lowest D_{10} value occurred when the tablets were made with PM and 12 kN compression force. When the tablets contained SD and 3% Mg-St, high D_{60} values were observed. In contrast, low D_{60} was predicted when the tablets were made of PM and 1% Mg-St (Figure 3b). TS was lower when the quantity of Mg-St was high (3%). The tablets with PM, 1% Mg-St, and 15% MCC resulted in high values for TS. However, the tablets with SD and 3% Mg-St had low TS values (Figure 3c). The SD tablets

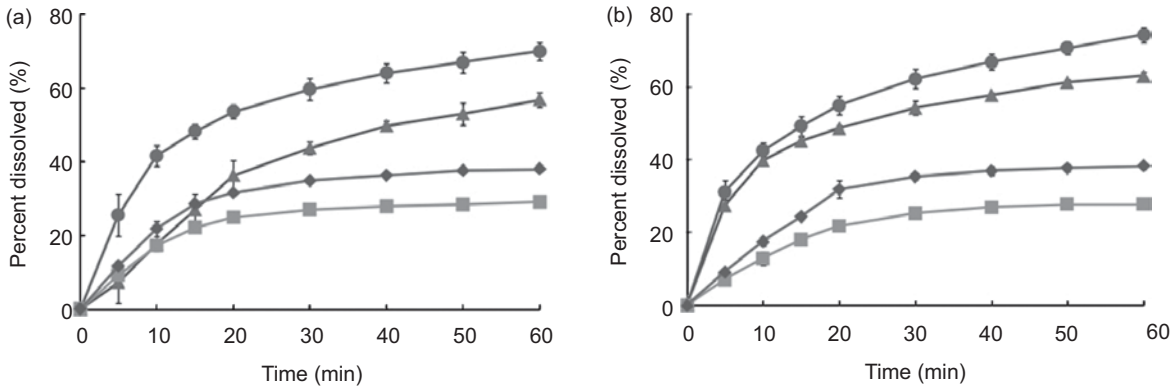

Figure 1. Typical examples of the dissolution profiles of IMC tablets. (▲) Rp.2, (●) Rp.7, (■) Rp.11, and (◆) Rp.13 (a) before and (b) after the accelerated test.

Table 1. Test formulations composed of five causal factors based on an L16 (2^5) fractional factorial experimental design and their response variables.

Rp.	Causal factors					Response variables			
	X_1	X_2 (%)	X_3 (%)	X_4 (%)	X_5 (kN)	D_{10} (%)	D_{60} (%)	TS (MPa)	f_2 (%)
1	SD	1	5	5	8	24.7 ± 2.0	49.7 ± 2.1	1.002 ± 0.065	41.5 ± 3.3
2	SD	1	5	15	12	17.6 ± 1.1	56.7 ± 1.9	1.337 ± 0.069	41.6 ± 1.0
3	SD	1	15	5	12	29.9 ± 3.1	63.6 ± 4.8	1.026 ± 0.068	58.5 ± 9.6
4	SD	1	15	15	8	36.0 ± 4.5	59.6 ± 1.9	1.093 ± 0.066	51.9 ± 1.8
5	SD	3	5	5	12	25.3 ± 0.8	67.8 ± 1.5	0.658 ± 0.119	53.5 ± 8.9
6	SD	3	5	15	8	41.6 ± 3.5	68.0 ± 2.4	0.447 ± 0.031	75.3 ± 9.6
7	SD	3	15	5	8	41.5 ± 2.8	69.8 ± 2.4	0.522 ± 0.041	72.7 ± 10.0
8	SD	3	15	15	12	19.6 ± 1.6	66.8 ± 4.5	0.601 ± 0.011	47.8 ± 3.3
9	PM	1	5	5	12	19.3 ± 1.9	30.5 ± 0.5	0.882 ± 0.065	82.2 ± 8.2
10	PM	1	5	15	8	21.4 ± 0.4	31.4 ± 0.5	0.844 ± 0.043	69.6 ± 0.9
11	PM	1	15	5	8	17.1 ± 1.5	29.1 ± 0.1	1.100 ± 0.095	78.0 ± 6.6
12	PM	1	15	15	12	18.9 ± 1.7	30.5 ± 0.7	1.480 ± 0.037	76.8 ± 2.8
13	PM	3	5	5	8	21.8 ± 2.0	37.9 ± 0.4	0.540 ± 0.118	79.3 ± 4.3
14	PM	3	5	15	12	20.4 ± 5.8	40.9 ± 4.3	0.770 ± 0.063	74.7 ± 5.0
15	PM	3	15	5	12	17.7 ± 2.2	38.7 ± 0.9	1.055 ± 0.103	74.9 ± 6.2
16	PM	3	15	15	8	21.2 ± 3.7	39.1 ± 0.3	1.017 ± 0.063	70.8 ± 7.3

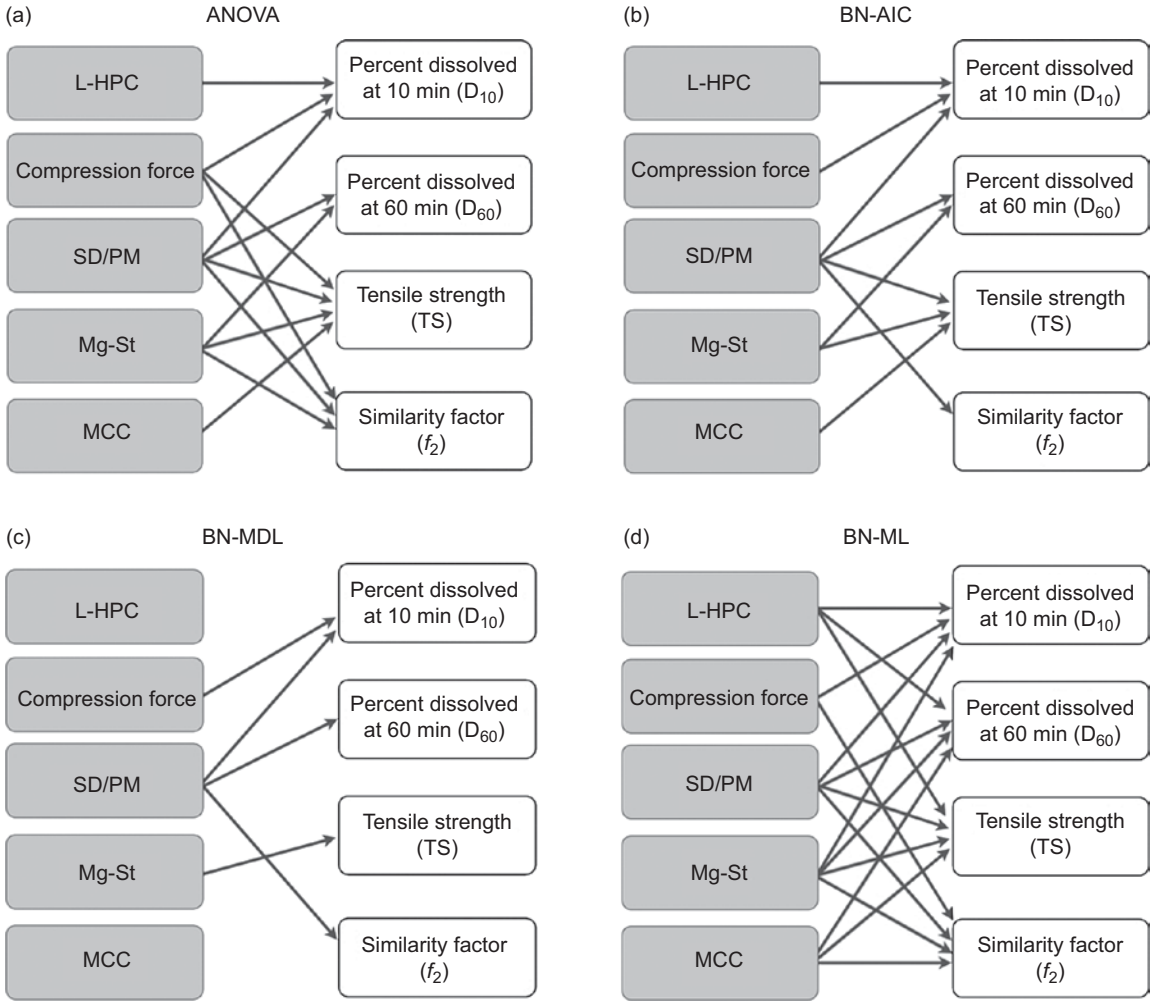

Figure 2. Network models between causal factors and responses estimated by (a) ANOVA and (B)–(D) BN models based on three judging standards (b) Akaike's information criterion (BN-AIC), (c) minimum description length (BN-MDL), and (d) maximum log likelihood (BN-ML). The nodes correspond to the causal factors and pharmaceutical responses, respectively, and the links represent the dependencies between them.

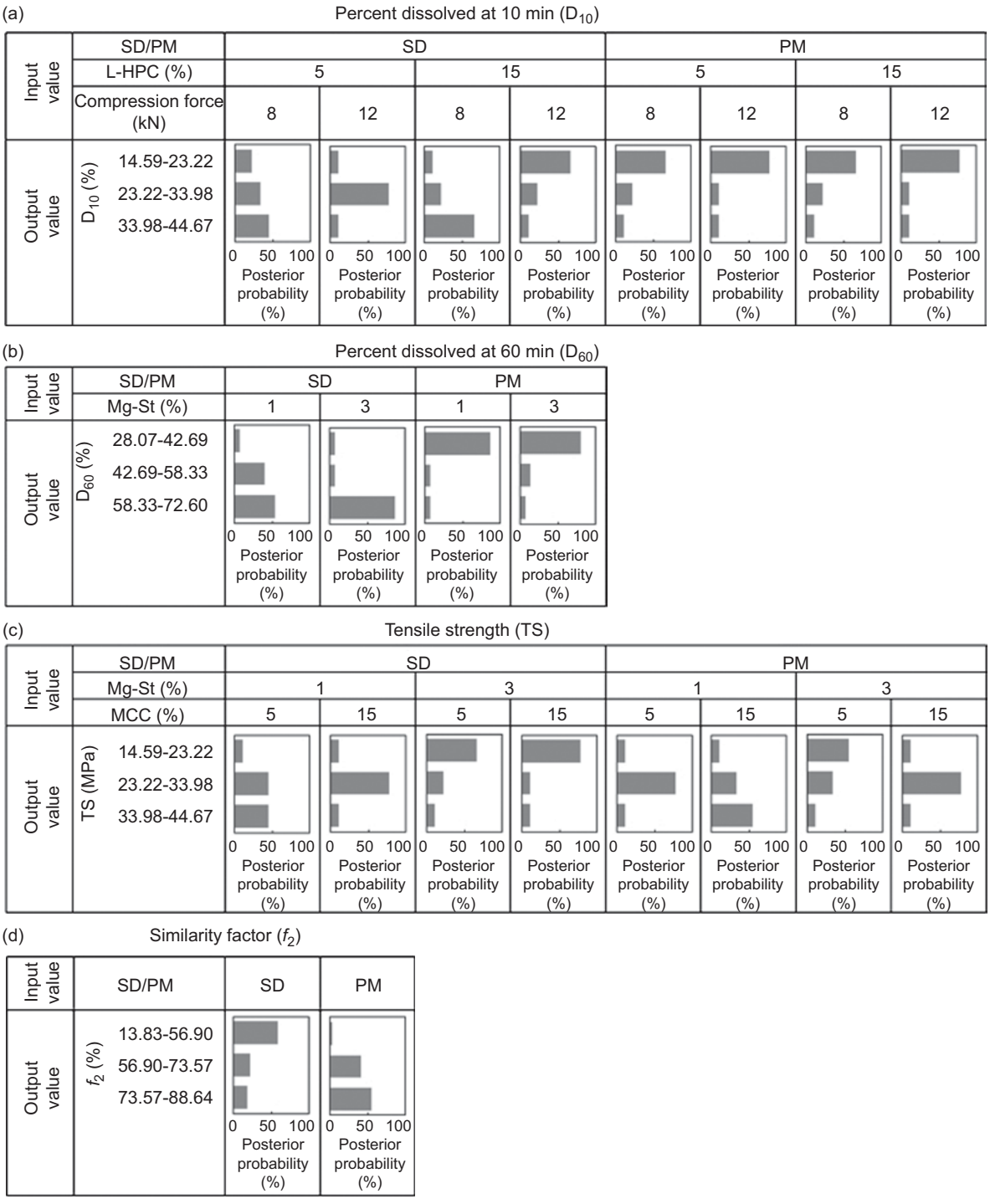

Figure 3. Conditional probability distributions (CPDs) of the pharmaceutical responses (a) D_{10}, (b) D_{60}, (c) TS, and (d) f_2 inferred by BN. Causal factors associated with each response are set as prior probabilities. CPDs of the responses are estimated for overall combinations of the causal factors.

showed a tendency for low f_2, whereas the PM tablets had high f_2 (Figure 3d). The dissolution profiles before and after the accelerated test were less similar when SD was used in the tablets.

With BN modeling, the posterior probability of the causal factors is also predicted using CPDs. To clarify the effects on D_{10} and D_{60}, the posterior probabilities of the causal factors were predicted from D_{10} and D_{60}. When the tablets had a low D_{60}, the BN model inferred a formulation with IMC PM. When the tablets had a low D_{10} and a high D_{60}, the BN model inferred a formulation with IMC SD, high quantities of Mg-St and L-HPC, and a high compression force. Conversely, when the tablets had a high D_{10} and a high D_{60}, the BN model inferred a formulation with IMC SD, large quantities of Mg-St and L-HPC, and a low compression force. Furthermore, the tablets that had

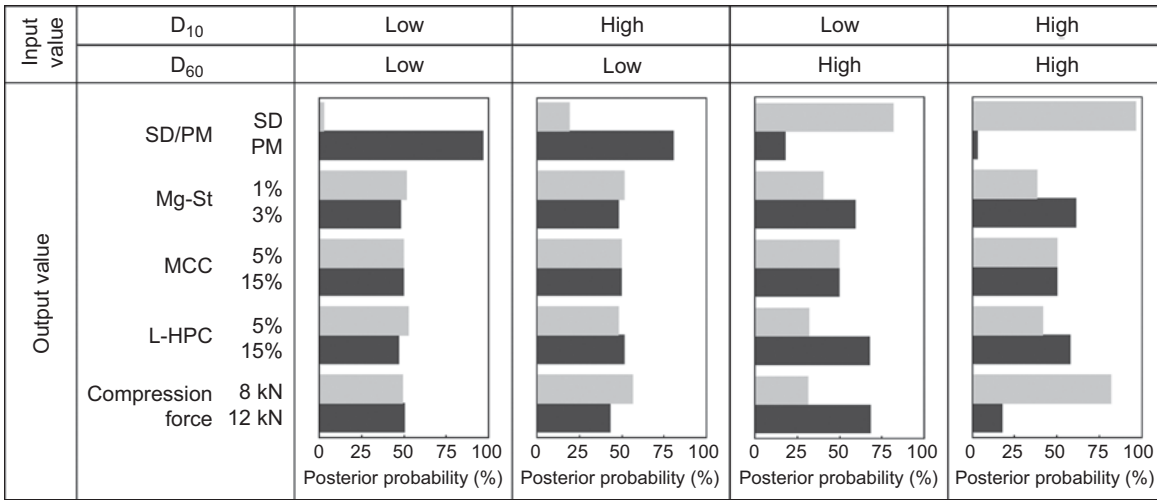

Figure 4. Conditional probability distributions (CPDs) of causal factors inferred by BN. Dissolution properties are set as the prior probabilities. The CPDs of the causal factors are estimated for four cases: low D_{10} and low D_{60}; high D_{10} and low D_{60}; high D_{10} and low D_{60}; and high D_{10} and high D_{60}.

low D_{10} and high D_{60} required a much higher compression force than did the tablets with high D_{10} and high D_{60} (Figure 4).

To predict an IMC tablet with excellent properties, i.e. high dissolution rate, high hardness, and stable storage properties, the posterior probabilities of the causal factors were predicted. IMC SD, low quantities of Mg-St and MCC, a high quantity of L-HPC, and 8 kN compression force were estimated to be the best combination of causal factors (Figure 5).

A leave-one-out cross-validation study was performed to evaluate the prediction accuracy of the BN model. The classification accuracies for D_{10}, D_{60}, TS, and f_2 were shown to be 83.3, 83.3, 77.1, and 62.5%, respectively, suggesting that the BN model classified the responses into each category well.

Discussion

In the development of pharmaceutical formulations, the relationships between causal factors and pharmaceutical responses are often complex. It is also difficult to determine these relationships quantitatively. A BN is a graphical probabilistic model consisting of nodes as the variables and links as the dependencies among the variables. In this study, a BN model was used to clarify the relationships underlying the causal factors and responses in IMC tablet formulations.

The D_{60} values of the IMC SD tablets were higher than those of the IMC PM tablets, whereas the D_{10} values of the IMC SD tablets were not always higher than those of the IMC PM tablets before the accelerated test. This result suggests that the SD state of IMC strongly affected D_{60}, although other factors were also important in improving the initial dissolution rate. Overall, the dissolution rate was better in the tablets containing IMC SD after the accelerated test.

An L16 (2^5) fractional factorial experimental design was used to estimate the relative intensities of the influences

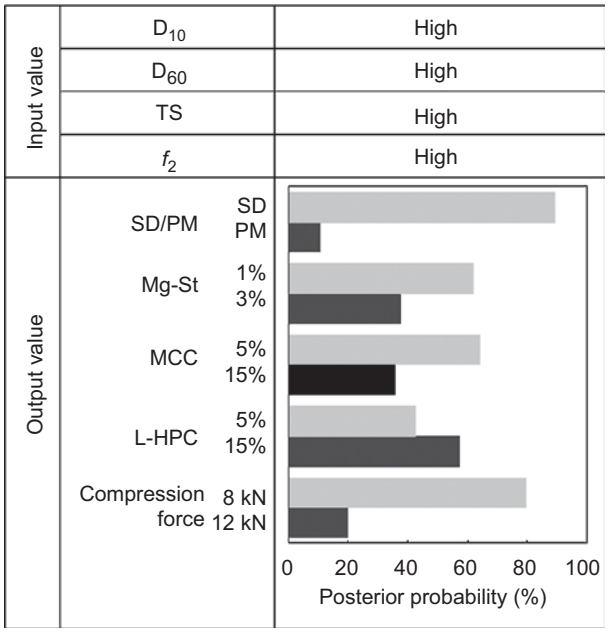

Figure 5. Conditional probability distributions (CPDs) of causal factors inferred by BN. CPDs of the causal factors were estimated for the best combination of response variables, such as high values for D_{10}, D_{60}, TS, and f_2.

of five causal factors on the tablet qualities. First, the data were analyzed by ANOVA. The initial dissolution rate, D_{10}, was strongly affected by X_1 (SD or PM). This suggests that the solubility of IMC and the disintegration of the tablets were higher in the IMC SD tablets than in the IMC PM tablets. Because the SD particle itself has very rapid dissolution properties, it is likely that the IMC SD tablet disintegrates easily. Therefore, the initial dissolution of the IMC SD tablets produced high values for D_{10}. The factors X_4 (L-HPC) and X_5 (compression force) were associated with D_{10} because L-HPC works as an effective disintegrant, and disintegration is also affected by the compression force. Similar results have been reported in

previous papers[16,17]. D_{60} was strongly affected by X_1 (SD or PM) and X_2 (Mg-St). In contrast, the TS value was affected by the factors X_1, X_2, X_3, and X_5. Among these, the effect of X_2 (Mg-St) was strongest. Mg-St reduces the interparticle binding strength, so the hardness of the tablet decreases as the quantity of Mg-St increases. More often than not, a reduction in the hardness of the tablet increases the dissolution rate.

To analyze the latent structure of the causal factors and responses in IMC tablets, BN models were constructed based on AIC, MDL, and ML as the judging criteria (Figure 2). All models showed that X_1 (SD or PM) affected D_{10}, D_{60}, and f_2; X_2 (Mg-St) affected TS; and X_5 (compression force) affected D_{10}. Furthermore, the BN modeling results were close to the results observed with ANOVA.

BNs efficiently implement the probabilistic inference algorithm, which estimates the probability distribution of arbitrary random variables in a model[18,19]. The CPDs of the responses of the IMC tablet were predicted using the BN model based on the AIC. When the tablets were composed of IMC SD, high values for both D_{10} and D_{60} were predicted, and vice versa. The effects of MCC and Mg-St on the TS values were observed with BN modeling. The posterior probabilities of the responses for various combinations of causal factors were appropriately estimated (Figure 3). The BN model was able to estimate not only the effects of the causal factors on each response but also the trends in the responses produced by the formulations as CPDs. The results indicate that BN models can reveal the relationships between the causal factors and responses in IMC tablet formulations. Regardless of changes in the D_{10} value, the tablets with a low D_{60} contained IMC PM. This suggests that D_{60} was strongly affected by whether the IMC was in the SD or PM form. The BN model implied that IMC SD, large quantities of Mg-St and L-HPC, and a compression force of 8 kN, in that order, were likely to increase D_{10} and D_{60}. Because L-HPC acts as an effective disintegrant, the initial dissolution is significantly influenced by the amount of L-HPC. Moreover, the compression force used in the manufacture of the tablets differed greatly between tablets with low and high D_{10} values, suggesting that the initial dissolution of IMC was also affected by the compression force (Figure 4).

The CPDs of the causal factors were investigated. To prepare tablets with excellent properties, low quantities of Mg-St and MCC, a large L-HPC component, and a low compression force are suggested (Figure 5). The BN technique can be used to predict formulations with excellent pharmaceutical properties.

Conclusion

The latent structure underlying the causal factors and responses of IMC tablets was modeled using the BN technique. The AIC-based BN model correlated strongly with the contribution ratio estimated with ANOVA. The complex relationships between causal factors and pharmaceutical responses were successfully determined using BN modeling. Moreover, both the causal factors and responses were predicted by the BN model using CPDs. This suggests that the combination of causal factors was predicted appropriately as posterior probabilities. We conclude that the BN technique is useful for understanding the latent structure underlying tablet formulations.

Declaration of interest

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