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Statistical Approach to Optimization of Drying Conditions for a Transdermal Delivery System

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ABSTRACT

The drying process is crucial in continuous manufacturing of matrix-type transdermal delivery systems (TDS) starting from solvent-based adhesives. In order to optimize the drying conditions of a TDS containing 22% of the partly volatile penetration enhancer 1,2-propanediol, the key factors drying time, which is reciprocal to the web speed, and drying temperature were optimized using the results of the statistical analysis of a two-factorial experiment. Thus, it was possible to reduce the amount of residual solvent ethyl acetate to below 0.02% while the 1,2-propanediol content of the TDS was kept at the desired 22% level.

INTRODUCTION

Matrix-type TDS consist of at least three main components, namely backing, matrix, and release liner (see Fig. 1). In most cases the matrix comprises nonvolatile components of a biocompatible pressure sensitive adhesive (PSA); the so-called adhesive solids; and the drug, which is normally dissolved or suspended within the matrix; and if necessary, a penetration enhancer.

Several types of adhesives, mainly polyacrylates, synthetic rubbers, and silicones, are employed for the manufacturing of TDS (1). Many commercially available PSA are either water-based dispersions or emulsions, or solutions of the polymers in organic solvents. Therefore a drying process is required within the manufacturing of matrix TDS, starting with the latter PSA.

This study deals with the manufacturing, especially the drying conditions of a matrix TDS, using a mixture

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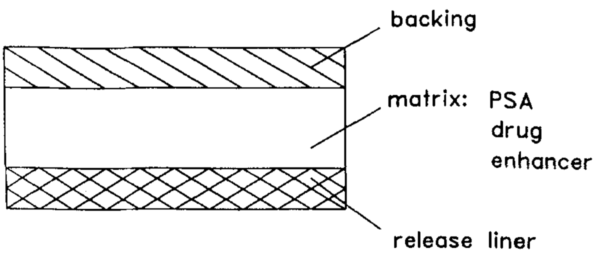

Figure 1. Cross section of a matrix TDS.

of a polyacrylate solution in ethylacetate (Gelva® 788) and the partly volatile penetration enhancer 1,2-propanediol (2,3). A simplified illustration of the applied equipment is given in Fig. 2.

During the early phase of process optimization, placebo runs were performed, on the assumption that the addition of a small amount of drug to the wet mix will not significantly alter the results obtained under placebo conditions.

The process factors "oven temperature" and "drying time" (which is proportional to the reciprocal web speed) were optimized using a statistical approach. The effects analyzed were "content of 1,2-propanediol," "content of ethylacetate," and "water content" of the resulting matrices.

Over the past decades, statistical methods have been employed more and more to support several fields of pharmaceutical interest including pharmaceutical process optimization (4). Especially response surface techniques have become popular in the recent past. Schofield et al. (5) and Chariot et al. (6) applied quadratic response functions to analyze the relationship between tablet properties and formulation process variables. Wehrlé et al. (7) also used a quadratic response function for a two-factorial design to obtain contour plots for the respective target variables. Although our statistical approach is close to theirs, our optimization process differs from the latter in that we were searching for a relative optimum for one target variable given a certain value for a second target variable.

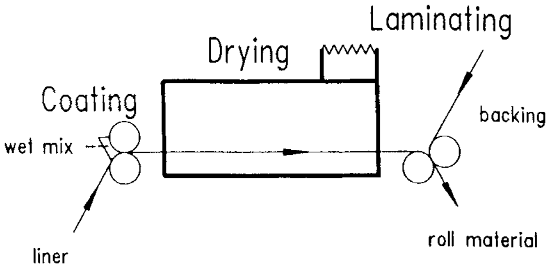

Figure 2. Continuous production of TDS roll material in principle.

The basic goal of this study was to evaluate drying conditions which result in a matrix containing 22% of the penetration enhancer 1,2-propanediol but only minimal amounts of the process solvent ethyl acetate and minimal amounts of water. To obtain these conditions, a quadratic function was fitted and optimized using the method of Lagrange multipliers (8) and the Newton–Raphson approach (9).

MATERIALS

Gelva 788 (50% solids in ethyl acetate) was supplied by Monsanto (Springfield, MA, USA). 1,2-Propanediol was obtained from Hüls (Witten, Germany) and ethyl acetate purchased from Merck (Darmstadt, Germany). A Saran®-Hytrel® coextrudate of Bertek Inc. (St. Albans, VT, USA) was used as backing, and siliconized poly(ethylene terephthalate) (PET) from the same supplier served as release liner.

METHODS

Manufacturing Process

First experiment: 1500 g Gelva 788, 403.8 g 1,2-propanediol, and 500 g ethylacetate were introduced into a 5-liter beaker and stirred for 1 hr using a propeller-equipped mixer. After a visual and a microscopical check of homogeneity, the obtained wet mix was coated onto the release liner by a knife overroll technique using a continuous laboratory coater (built by Bertek Inc., St. Albans, VT, USA) at nine different drying conditions (see Table 1). The achieved coating weight was 50 ± 5 $g \cdot m^{-2}$. The resulting material was subsequently laminated with the backing and die cut into 10-cm^2 patches of circular shape.

Using the same technique a second, independent experiment was performed starting from half of the amount of wet mix and coating at five different drying conditions (see Table 2).

Analytical Methods

Six samples of 10 cm^2 each from the material obtained under the 14 different drying conditions were weighed and then sonicated in 40 ml acetonitrile. The resulting suspensions were adjusted to 50 ml with ace-

Table 1

Influence of Drying Conditions on the Content of Volatile Components in Matrix TDS, Data of the First Experiment

Drying Condition	Temperature (°C)	Drying Time (sec)[a]	1,2-Propanediol Content (%)[b]	Ethyl acetate Content (%)[b]	Water Content (%)[b]
1	60	118	25.5 (0.6)	0.048 (0.006)	3.62 (0.12)
2	60	88.5	29.7 (0.6)	0.150 (0.020)	3.41 (0.20)
3	60	70.8	29.3 (1.0)	0.192 (0.080)	3.92 (0.15)
4	70	70.8	28.4 (1.0)	0.123 (0.011)	3.54 (0.23)
5	70	88.5	26.3 (0.6)	0.069 (0.009)	3.43 (0.14)
6	70	118	21.3 (0.6)	0.033 (0.000)	2.86 (0.07)
7	80	118	15.3 (0.7)	0.027 (0.006)	2.41 (0.22)
8	80	88.5	17.6 (1.3)	0.032 (0.000)	2.56 (0.10)
9	80	70.8	22.5 (0.8)	0.094 (0.012)	2.96 (0.23)

[a] The related web speeds are: 45 cm · min^{-1} (118 sec), 60 cm · min^{-1} (88.5 sec), and 75 cm · min^{-1} (70.8 sec).

[b] All values are related to the sample weight and given as mean (*SD*) for $n = 6$.

tonitrile and analyzed for content of 1,2-propanediol and ethyl acetate, applying two different gas chromatographic (GC) methods. The GC system for quantification of 1,2-propanediol was an integrated system consisting of an automatic sampler (HP 7673) and a gas chromatograph (HP 5890) equipped with a flame ionization detector. The stationary phase was a reversed-phase capillary column CP-SIL CB5, 10 m × 530 μm ID (Chrompack) while helium served as carrier gas at a flow rate of 2.5 ml·min^{-1}. Temperature was kept isothermal at 70°C. 1,2-Propanediol showed a retention time of 2.5 min.

A similar GC system was applied for analysis of ethyl acetate, but a packed glass column was introduced: 15% Triton X 305 and 1.5% KOH on Chromosorb W (80–100 mesh), 2 m × 1 mm ID. Helium was used as carrier at a flow rate of 30 ml·min^{-1}. The retention time of ethylacetate was 2.3 min.

The measurements were carried out using 1,2-propanediol and ethylacetate, respectively, as external standards. All samples and standards were injected at a volume of 1 μl.

Additionally, 6 10-cm^2 samples of the above-mentioned material were weighed and subsequently disintegrated in 5 ml chloroform. Aliquots of the obtained solutions were used for the determination of water content according to Karl Fischer, using a Mitsubishi CA 02 moisture meter.

Table 2

Comparison of Contents of Volatile Components in Matrix TDS, Predicted vs Obtained

Drying Condition	Temperature (°C)	Drying Time (sec)[a]	1,2-Propanediol Content (%)[b] Predicted	1,2-Propanediol Content (%)[b] Obtained	Ethyl acetate Content (%)[b] Predicted	Ethyl acetate Content (%)[b] Obtained	Water Content (%)[b] Predicted	Water Content (%)[b] Obtained
10	65	135	22.3	20.6 (0.6)	0.025	0.017 (0.001)	3.46	3.82 (0.18)
11	65	120	24.1	22.6 (0.3)	0.035	0.018 (0.001)	3.31	4.26 (0.14)
12	67	127.5	22.3	22.2 (1.3)	0.025	0.018 (0.001)	3.27	4.06 (0.14)
13	69	135	20.3	19.0 (0.6)	0.021	0.015 (0.002)	3.24	3.82 (0.18)
14	69	120	22.3	19.9 (0.6)	0.025	0.016 (0.002)	3.12	4.00 (0.10)

[a] The related web speeds are: 39.33 cm · min^{-1} (135 sec), 41.65 cm · min^{-1} (127.5 sec), and 44.25 cm · min^{-1} (120 sec).

[b] All values are related to the sample weight and given as mean (*SD*) for $n = 6$ ($n = 3$ in the case of ethyl acetate data).

Statistical Approach

The main goal of the experiments was to find drying conditions resulting in a 22% 1,2-propanediol content while keeping the ethyl acetate and water percentages as low as possible.

Therefore, in a first step to approximate the relationship between 1,2-propanediol on one side and temperature and drying time on the other, a quadratic function

$$f(t, s) = a + b_1 t + b_2 s + b_{11} t^2 + b_{22} s^2 + b_{12} ts$$

was fitted by the least squares method to the 1,2-propanediol data (t denotes temperature and s the drying time). From this the estimated 22% contour line was evaluated.

In a second step another quadratic function, $g(t, s)$, depending on temperature and drying time, was fitted to the observed ethyl acetate percentages. The minimum value of this function g on the 22% contour line was calculated as described below. The corresponding combination (t_0, s_0) of temperatures and drying time where this minimum was attained, was the drying condition of interest.

To find the minimum value (t_0, s_0) of interest, the method of Lagrange multipliers (9) was used. Let $f_1(t, s)$ and $f_2(t, s)$ denote the derivatives of $f(t, s)$ with respect to t and s; i.e.

$$f_1(t, s) = b_1 + 2b_{11} t + b_{12} s,$$

$$f_2(t, s) = b_2 + 2b_{22} s + b_{12} t$$

and let a corresponding notation hold for g. Then in order to find the minimum value, one has to solve the set of equations

$$g_1(t, s) + \lambda f_1(t, s) = 0$$

$$g_2(t, s) + \lambda f_2(t, s) = 0$$

$$f(t, s) - 22 = 0$$

for t, s, and λ. This was done iteratively applying the Newton-Raphson approach (10).

The same procedure was applied to find the process parameters which minimize the water content. For the calculations, the Statistical Analysis System (SAS) (10) was used.

RESULTS AND DISCUSSION

The results of the first experiment are given as mean values in Table 1. The quadratic functions estimated from these data are presented as contour plots in Figs. 3, 4, and 5. The 22% 1,2-propanediol contour line is included in the ethyl acetate and water plots as additional information.

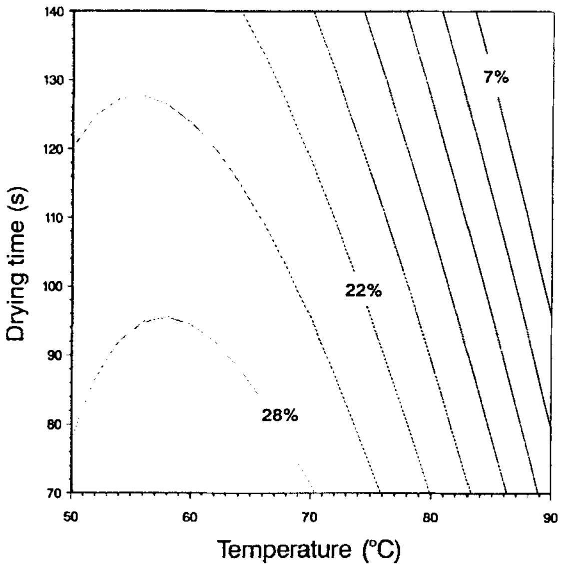

Figure 3. Content of 1,2-propanediol as a function of drying time and temperature. The contour lines represent equidistant contents of 1,2-propanediol (step size 3%).

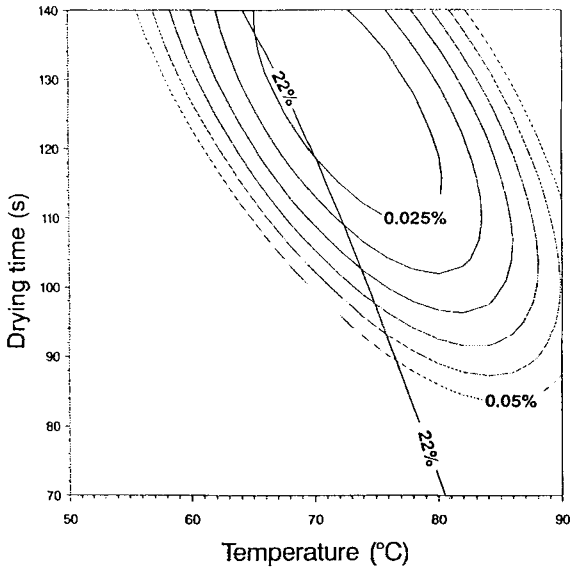

Figure 4. Content of ethyl acetate as a function of drying time and temperature. The contour lines represent equidistant contents of ethyl acetate (step size 0.005%). The 22% 1,2-propanediol contourline is included.

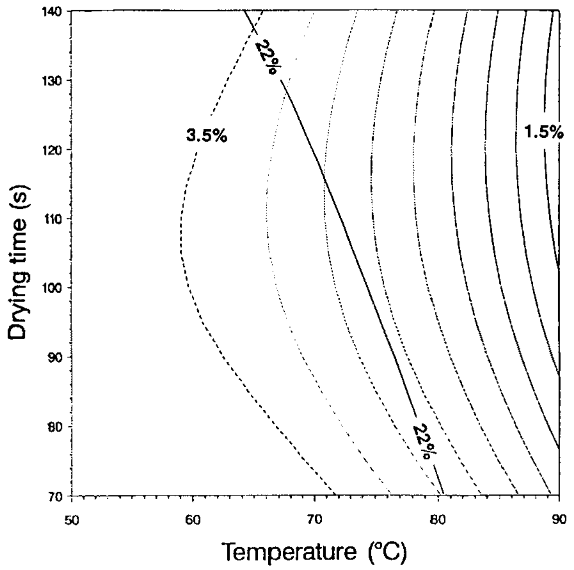

Figure 5. Content of water as a function of drying time and temperature. The contour lines represent equidistant contents of water (step size 0.25%). The 22% 1,2-propanediol contour line is included.

It should be noted that the data only reflect intraprocess variation which is induced by the analytical procedure, irregularities during the process, and measurement errors. Interprocess variation is not taken into account, since the process was not repeated for costs and capacity reasons.

The values obtained from the analysis indicated a reasonable fit for the 1,2-propanediol data (= 0.85) but more or less poor fits for the other two variables (0.41 for ethyl acetate and 0.56 for water).

In addition, the fitted functions turned out to be extremely unrobust with respect to slight changes in the parameters, for example, due to rounding. All this had to be kept in mind interpreting the results.

The minimum value of ethyl acetate on the 22% 1,2-propanediol contour line predicted from the fitted model is 0.024%. The drying condition that corresponds to this value is a temperature of 67.5 °C and a drying time of 128.4 sec. For water the corresponding values are 2.85% at 75.5 °C and 93.2 sec.

A second experiment was then run to get an impression as to whether the above results were of global interest. Therefore, five additional drying conditions around the minimum point (67.5°C, 128.4 sec) with respect to ethyl acetate estimated from the first experiment were selected for the second experiment. The data obtained by the latter experiment are given in Table 2 together with the predicted values from the model obtained from the first experiment.

Estimators of the interprocess variation were obtained as the mean of the squared "observed minus predicted" differences times ½ from Table 2 and were compared to the estimators of the intraprocess variation from the regression analysis of the first experiment. For 1,2-propanediol and water the interprocess variation proved to be greater than the intraprocess variation caused by measurement errors and so forth (1,2-propanediol: 1.25 vs. 0.80; water 0.27 vs. 0.02). For ethyl acetate the intraprocess variation proved to be greater than the interprocess variation (0.0008 vs. 0.0001).

Taking into consideration the unrobustness of the fitted models from the first experiment, the agreement between the predicted and observed values is satisfactory. Drying condition No. 12 of the second experiment (67°C, 127.5 sec) was of special interest because it was closest to the estimated optimal drying condition (67.5°C, 128.4 sec). Here a very good agreement between predicted and observed was found with respect to 1,2-propanediol and ethyl acetate.

CONCLUSION

As expected, extending the drying time as well as raising the temperature generally leads to lower contents of volatile components in the matrix, as can be seen easily in Figs. 3 to 5. However, it is possible to minimize the content of ethyl acetate in the matrix while the content of 1,2-propanediol is kept approximately at the required content of 22%. A comparison of the data of drying conditions No. 6 (118 sec at 70°C) and No. 9 (70.8 sec at 80°C) shows that matrices containing nearly the same level of the enhancer 1,2-propanediol differ in their load of residual solvent ethylacetate by the factor 3 (refer to Table 1). However, the maximum difference related to water content is much lower (refer to Table 1). Therefore it seems to be of minor practical importance.

The statistical approach to find the optimal drying conditions of a TDS with respect to minimal ethyl acetate content at a content of 22% 1,2-propanediol proved to be successful in that the predicted values were reproduced satisfactorily in a second experiment.

For future applications of the statistical method, further improvements are possible by increasing the number of drying conditions and, more important, by basing the predictions on replicated experiments.

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