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Research Article

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Preformulation Considerations for Controlled Release Dosage Forms: Part III. Candidate Form Selection Using Numerical Weighting and Scoring

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Abstract. Two numerical methods, Decision Analysis (DA) and Potential Problem Analysis (PPA) are presented as alternative selection methods to the logical method presented in Part I. In DA properties are weighted and outcomes are scored. The weighted scores for each candidate are totaled and final selection is based on the totals. Higher scores indicate better candidates. In PPA potential problems are assigned a seriousness factor and test outcomes are used to define the probability of occurrence. The seriousness-probability products are totaled and forms with minimal scores are preferred. DA and PPA have never been compared to the logical-elimination method. Additional data were available for two forms of McN-5707 to provide complete preformulation data for five candidate forms. Weight and seriousness factors (independent variables) were obtained from a survey of experienced formulators. Scores and probabilities (dependent variables) were provided independently by Preformulation. The rankings of the five candidate forms, best to worst, were similar for all three methods. These results validate the applicability of DA and PPA for candidate form selection. DA and PPA are particularly applicable in cases where there are many candidate forms and where each form has some degree of unfavorable properties.

KEY WORDS: candidate form selection; decision analysis; potential problem analysis.

INTRODUCTION

The development candidate form selection model described in Part I was a logical method that facilitated the selection of the free base form on McN-5707 (Fig. 1) from among eight forms. The eight forms were characterized with respect to critical factors for candidate selection. Forms were eliminated from further testing and consideration if a test result was unsatisfactory or problematic. The free base was selected from a final group that included the fumarate and maleate salts. The molecular weight (MW) conversion factors (CFs), i.e., ratio of MW of the salt form to the MW of the free form, were also considered in the final selection. This logical method works well when there are a limited number of candidate forms and the number can be further reduced to a reasonable number for final selection. This method does not lend itself to cases where there is difficulty in selection due to there being many candidate forms, and where there are problematic properties in all of the candidate forms.

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Decision Analysis (DA) and Potential Problem Analysis (PPA) appeared to be suitable alternatives to the logical method applied in Part I. In the absence of a published comparison between DA and/or PPA and the simpler logical selection model, we decided to make a comparison of the results from these three models.

DA and PPA are scoring and weighting process models. Walkling and Appino (1) first applied DA and PPA to salt form selection. The concepts for these models are derived from models developed by Kepner and Tregoe (2). DA requires assignment of a weight to the attribute and a score for the result or outcome. It utilizes every available attribute, applied to all candidate forms. The weighted scores are summed and selection is made from among those with the higher total scores. PPA requires assignment of a seriousness factor and probability for each potential problem. PPA simplifies the analysis by reducing the number of properties considered. Potential problems related to a common property are grouped together to reduce the impact. The total sums of the probability-seriousness products are calculated for each form, and final selection is made from among the forms with the lowest scores. Normally selection is made from among the group of higher DA scores and lower PPA scores. The accuracy is not based on highest and lowest scores. DA and PPA may be applied to the same data, and the selection may be based on a consensus of scores from the two procedures.

Part I generated complete data sets for the fumarate, maleate and free base forms of McN-5707. In order to create

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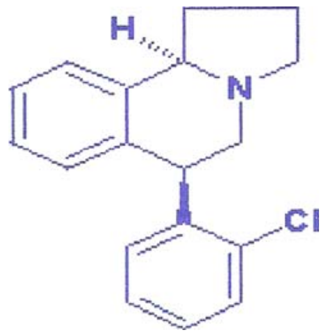

Fig. 1. Structure of McN-5707 (free base)

an opportunity for the comparison of the methods, the hydrochloride and phosphate hydrate forms were subjected to additional testing to complete the data set for a total of five forms.

MCN-5707 FORM SELECTION

Previously reported data (3) for five forms of McN-5707, the free base, and the hydrochloride, phosphate hydrate, fumarate and maleate salt forms were used. CFs and missing data for hydrochloride and phosphate hydrate salt forms were acquired by additional testing to create a complete the data set for five forms. The physical-chemical properties used were

- (a) Organoleptics, color, appearance and CF;
- (b) Crystallinity and melting behavior;
- (c) Critical solubilities, water, 0.1 N hydrochloric acid, and Simulated Intestinal Fluid (SIF) pH 7.5 at ambient room temperature (RT);
- (d) Hygrodynamics, percent weight change after
  - (i) Drying at 49°C/24 hours, and
  - (ii) Storage at RT for 1 week at extremes of humidity, 11% RH and 83% RH;
- (e) Processability
  - (i) Filming and sticking on compression, and
  - (ii) Rusting of a meehanite test bar after abrasion with the NCE powder followed by exposure to high RH at RT.

DECISION ANALYSIS

Eight veteran formulators, including bench level and senior managers, weight-ranked the importance (100 points total) of 13 physical-chemical properties, color and appearance, CF, melting range, crystallinity/XRD, gain/loss of moisture at RT/83% RH and at RT/11% RH, physical stability at 30°C/60% RH and at 40°C/75% RH, filming-sticking on compression, bulk density, and solubilities in 0.1 N hydrochloric acid, water, and SIF (pH 7.5). Means were calculated for each of the weight factors. The physical-chemical properties were independently reviewed and scored using a 0 to 10 grade, 10 being the highest score. The respective individual scores were multiplied by the weighting factors to obtain weighted scores and summed to obtain total weighted scores. The salt forms were then ranked highest to lowest. Selection of optimal forms was made from among the higher scores.

POTENTIAL PROBLEM ANALYSIS

The formulators also rated the seriousness (50 points total) of five potential formulation problems, filming-sticking, moisture sorption, XRD and DSC detected problem, solubilities, and salt form. A mean seriousness was calculated for each potential problem. The probabilities (0 to 1, 1 being the highest) of each potential problem were estimated independently from a review of the collected data. The respective probabilities were multiplied by the mean seriousness to obtain seriousness-probability products. The seriousness-probability products were totaled and ranked from lowest to highest. Selection of optimal forms was made from among the lower scores.

The polling survey was intended to be all encompassing. Some of the physical-chemical properties and potential problems that were rated in the polling of the formulators were not used in the evaluations of this NCE's forms. Rusting potential was omitted from the original poll. It was assigned the same weight as filming on compression because both problems were resolved in our laboratories using the same formulation process.

RESULTS

Decision Analysis and Potential Problem Analysis

Tables I and II provide a complete summary of the weighting and seriousness factors obtained from the polling of the eight experienced formulators. The data provided includes the individual, mean, minimum and maximum values obtained for each physical-chemical property. There is appreciable variance in the minimum and maximum values assigned by each of the formulators, dependent upon their experience and level of responsibility. In some instances it might be more practical to use the values associated with the formulators assigned to the project at hand. However, for this example mean values were employed to further reduce bias. Physical stability testing was omitted from the McN-5707 preformulation testing, and is not included in the salt selection process for this NCE. However, it has been employed in other salt selection problems. One of the conditions applied to the selection process for this compound was that minimal supplies of each form would be available. The physical stability of a capsule containing a DS form has been applied to other form selection processes. The applicability of a physical stability test comes from the use of capsules in blinded clinical trials, even when the final dosage form is intended to a tablet.

McN-5707

The physical-chemical properties of the free base, hydrochloride, phosphate hydrate, fumarate and maleate forms of McN-5707 are presented in Table III. Table IV lists the scores, weights, weighted scores and total scores needed for applying the DA model to selecting an optimal form for McN-5707.

Table V lists the seriousness factors, probabilities, seriousness-probability products and totals needed for applying the PPA model to selecting an optimal form of McN-5707. The

Table I. Results from a Poll of Eight Formulators to Assess Weighting Factors for Use in Decision Analysis

	Formulator										
Physical-Chemical Properties	1	2	3	4	5	6	7	8	Mean	Min.	Max.
Organoleptics											
Color, appearance	2	2	5	3	4	5	3	5	3.625	2	5
Correction Factor (CF)	6	10	9	3	6	1	0	5	5.0	0	10
Crystal Properties											
DSC and Melting Range	2	9	10	8	7	18	15	12	10.125	2	18
XRD	5	5	10	10	6	5	0	4	5.625	0	10
Hygrodynamics											
Gain/loss at 25°C 83%RH	4	5	7	9	11	4	15	3	7.25	3	15
Gain/loss at 25°/11% RH	8	5	7	9	5	5	0	3	5.25	0	9
Physical Stability in Capsule											
4 weeks at 30°C/70%RH	20	10	9	10	11	15	25	5	13.125	5	25
4 weeks at 40°C/70%RH	10	5	9	7	7	10	3	5	7.0	3	10
Processability											
Filming/Sticking	7	13	5	15	10	17	15	20	12.75	5	20
Bulk Density	3	5	5	6	7	5	7	20	7.25	3	20
Solubilities											
0.1 N Hydrochloric acid	20	13	8	13	9	5	7	6	10.125	5	20
Water	8	13	8	7	10	5	7	6	8.0	5	13
SIF, pH 7.5	5	5	8	0	7	5	3	6	4.875	0	8
Totals (Score)	100	100	100	100	100	100	100	100	100.0		

ranking from DA (Table IV) is fumarate 685 points > maleate 670 points > free base 653 points > phosphate hydrate 614 points > hydrochloride 547 points. The ranking from PPA (Table V) is fumarate 4.663 points < maleate 5.813 points < free base 8.775 points << phosphate hydrate 21.448 points < hydrochloride 29.65 points. The accuracy of these two models is such that selections are usually made from among those with the best scores. The logical selection model ranked the free base, maleate and fumarate as preferred forms. The free base, fumarate and maleate salt forms have the best scores from all three models. Using both DA and PPA to obtain a consensus would have arrived at the same selection of the free base, fumarate and maleate as optimal forms.

CONCLUSIONS

This example demonstrates the applicability of DA and PPA to candidate form selection problems. All three methods were in agreement ranking the free base, fumarate and maleate forms as optimal form choices. Our laboratory has used these numerical modeling methods for more complicated problems such as the identification of optimal forms in an instance where 13 forms were evaluated with no logical choices due to varying problematic properties in multiple characterization tests.

The use of mean values for model factors obtained from a number of experts rather than from one or a few was also shown to be an advantage, even though a comparison of the mean values with the individual values from formulators were not presented.

Interactiveness

Tables I, II, III, IV and V are spreadsheets. Readers are invited to explore the use of DA and PPA with the data presented. Scores, probabilities, weights and seriousness

Table II. Results from a Poll of Eight Formulators to Assess Seriousness Factors for Use in Decision Analysis

	Formulator										
Potential Problem	1	2	3	4	5	6	7	8	Mean	Max.	Min.
Filming/Sticking	5	15	6	10	13	15	8	20	11.5	5	20
Moisture Sorption	15	15	9	15	11	10	12	5	11.5	5	15
Crystallinity (XRD/DSC)	5	8	12	10	7	15	12	10	9.875	5	15
Solubility	20	9	10	10	13	5	8	10	10.625	5	20
Salt Form	5	3	13	5	6	5	10	5	6.5	3	13
Total	50	50	50	50	50	50	50	50			

Table III. Physical-Chemical Properties of Five Forms of McN-5707

Test →		XRD	MP	Hygrodynamics, % Change			Solubility at 25°, as free base, mg/mL			Corrosivity	Filming-Sticking
					24°/1	wk/RH					
Form ↓	CF	cryst	start °C	49°/24 h	11%	83%	0.1HCl	H_20	SIF	Obs'n	Obs'n
Free Base	1.0	Yes	95	−0.18	−2.6	0.0	24.8	0.004	0.004	None	Slight
HCl	1.13	Yes	95	−2.3	−1.8	−5.7*	0.30	30.0	0.088	>Severe	Severe
Phosphate hydrate	1.41	No	189	+0.60	0.7	1.8	23.7	9.14	0.009	None	Slight
Fumarate	1.41	Yes	191	−0.03	−0.04	0.03	12.7	1.75	0.009	None	<Slight
Maleate	1.41	Yes	157	−0.11	−2.2	0.04	8.63	3.16	0.012	None	Slight

*Observed a physical change, powder to glass

Table IV. Application of Decision Analysis to Salt Form Selection for McN-5707 Using Physical-Chemical Data and Outcomes Reported in Table III

		Free Base		Hydrochloride		Phosphate Hydrate		Fumarate		Maleate	
Physical-Chemical Properties	Weight	Score	WT x Score	Score	WT x Score	Score	WT x Score	Score	WT x Score	Score	WT x Score
Organoleptics											
Color, Appearance	3.625	10	36.25	10	36.25	10	36.25	10	36.25	10	36.25
Correction Factor, CF	5	10	50	10	50	7	35	5	25	5	25
Crystallinity											
Capillary Melting Range	10.125	9	91.125	8	81	10	101.25	10	101.25	10	101.25
XRD	5.625	10	56.25	10	56.25	0	0	10	56.25	10	56.25
Hygrodynamics											
Gain/loss at 83%RH/25°C	7.25	10	72.5	2	14.5	6	43.5	10	72.5	10	72.5
Gain/loss at 11%RH/25°C	5.25	5	26.25	6	31.5	4	21	10	52.5	10	52.5
Processability											
Filming/Sticking	12.75	8	102	5	63.75	8	102	9	114.75	8	102
Corrosivity	12.75	10	127.5	4	51	10	127.5	10	127.5	10	127.5
Critical Solubilities											
0.1 N Hydrochloric Acid	10.125	9	91.125	9	91.125	9	91.125	9	91.125	8	81
Water	8	0	0	9	72	7	56	1	8	2	16
SIF, pH 7.5	4.875	0	0	0	0	0	0	0	0	0	0
Totals	92.375		653		547		614		685		670

Table V. Application of Potential Problem Analysis to Salt Form Selection for McN-5707 Using Physical-Chemical Data and Outcomes Reported in Table III

	Seriousness	Free Base		Hydrochloride		Phosphate Hydrate		Maleate		Fumarate	
Potential Problems	S	P	PxS	P	PxS	P	PxS	P	PxS	P	PxS
Salt Form	6.5	0.0	0.00	0.0	0.00	0.2	1.3	0.2	1.30	0.2	1.3
Moisture	11.5	0.2	2.3	1.0	11.5	0.6	4.6	0.2	2.30	2.3	0.00
Crystallinity	9.875	0.1	0.988	0.1	0.988	1.0	9.88	0.0	0.00	0.0	0.00
Filming/Sticking	11.5	0.2	2.3	0.6	6.9	0.2	2.3	0.1	1.15	0.2	2.3
Corrosivity	11.5	0.0	0.00	0.8	9.2	0.0	0.00	0.0	0.00	0.0.	0.00
Solubility	10.625	0.3	3.188	0.1	1.062	0.1	1.063	0.1	1.063	0.1	1.063
Total	61.5		8.775		29.65		21.448		5.813		4.663

factors can be changed. Similarly, new values from new surveys and new selection problems, real or hypothetical, can be substituted into the various tables for application to new salt selection problems.

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