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Research Article

Theme: Team Science and Education for Pharmaceuticals: the NIPTE Model
Guest Editors: Ajaz S. Hussain, Kenneth Morris, and Vadim J. Gurvich

Decision Support for Excipient Risk Assessment in Pharmaceutical Manufacturing

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Abstract. Excipients have always been a key input into pharmaceutical products, profoundly affecting product quality. Currently, most of our knowledge of excipient critical quality attributes is empirical, gained through experience, and shared through publications and other sources. The behavior of excipients is complicated, with many different failure modes that depend on the type of dosage form. Even within the same dosage form, there can be multiple failure modes depending on the manufacturing method. This complex behavior creates many possible combinations to assess when designing a formulation or evaluating regulatory submissions. Formulation science could be improved if data from different sources could be made widely available through an interactive system using a consistent, structured format to help formulators and regulators assess the risk of excipient usage for a particular dosage form with a particular manufacturing method. This paper describes a decision support system that was created for assessing excipient risk in different types of formulations and considering different types of manufacturing methods, dosage forms, and excipient functionality. The Excipient Risk Assessment System consists of a database that stores knowledge about factors that affect formulation design and a decision support processor that manages selections for creating formulation scenarios and assigning risk. Formulation and risk assessment data are provided by formulation science experts. This enables the system to assess compatibility among excipients, functionality, dosage forms, and manufacturing methods selected for formulations. The interface guides users through the creation of formulation scenarios and displays customized, interactive risk assessment reports for users to search and explore.

KEY WORDS: risk assessment; excipient; excipient functionality; formulation; pharmaceutical manufacturing; decision support.

INTRODUCTION

The Quality Target Product Profile (QTPP) lays out the quality characteristics a drug product should ideally have to be safe and therapeutically effective (1–3). To achieve this goal, pharmaceutical products must be carefully designed to have characteristics such as desired release rate, stability, manufacturability, and palatability. These properties are engineered into the product *via* the formulation, which is comprised of the active pharmaceutical ingredients (API) and the excipients. Thus, for safe and effective products, excipient selection is critical.

The selection of excipients for a formulation is a combination of art and science. Unfortunately, most of our knowledge about the relationships between excipients and product performance is empirical and is gained through many years of experience. Dosage forms and the pharmaceutical industry are evolving at an ever-increasing pace, making access and use of empirically gathered data more difficult for formulation development. For example, many of the drugs coming out of discovery today are poorly soluble, creating tremendous formulation challenges and leading to the establishment of amorphous solid dispersions (ASD) as an important method of formulation (4). Other key factors such as the move from batch to continuous manufacturing, the growing importance of biotech products, improved processing equipment with ever higher rates of production, and the growth of the generic industry with their extremely tight development timelines all impose greater demands on formulation development and make appropriate selections of excipients more challenging and more critically important.

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Excipient selection is a complex task in which formulators must examine many factors to make good choices. Below are some of the essential factors that need to be considered when developing a formulation:

- *What type of dosage form will be produced?* For example, a tablet may be for traditional oral use, for buccal and sub-lingual, orally disintegrating, chewable, effervesce, vaginal, completely soluble use, or for use as implants in veterinary products. The types of excipients selected depend on the environment where the tablet is administered. Excipients used to produce tablets designed for release in the small intestines would be different from excipients used to produce orally disintegrating tablets (ODT) designed for release in the mouth or tablets designed for release as an implant in cattle.
- *What type of excipient functionality is needed to ensure that the dosage form has the required performance characteristics?* Is the excipient a filler-binder, disintegrant, lubricant, coating agent, suspending agent, surfactant, or viscosity-enhancing agent? Many different types of functionality are needed to successfully produce a dosage form. In addition, excipients can have different functionalities in the same dosage form. For example, starch can have the role of wet granulation binder and disintegrant in the same dosage form.
- *What type of manufacturing method will be used?* When filler-binder functionality is required, different types of excipients would be selected for wet granulation *vs* dry granulation *vs* direct compression. For these different scenarios, different excipient grades have been created to optimize performance for different methods of manufacture. Understanding how to best use all the different excipient grades requires considerable effort and experience.
- *What type of release rate is needed?* Examples of release rates that affect excipient selection are immediate release (IR), controlled release (CR), delayed release, enteric release, and colonic release. Each of these release rates has different grades that have been developed and optimized to produce the desired product performance.
- *What is the target patient population?* Some excipients, such as the glycols, work well in adult population but are toxic to children, and geriatric patients are often achlorhydric, which can affect drug absorption (1–5). In addition, there are species differences, such as canine medications which must have different resting pH and gastric motility (1).
- *Are there interactions between the excipient and the API?* For example, some APIs are sensitive to oxidation. Some synthetic excipients, such as povidone, can have trace amounts of peroxides that result from the excipient synthesis, and the peroxide level can affect long-term product stability. The same is true for other excipient properties such as moisture levels and excipient pH. These trace or residual properties can drastically affect the long-term stability of a dosage form.

Given the many complex excipient functional requirements needed to make a successful dosage form, excipient suppliers have developed a wide range of excipients, with each excipient type having a wide range of grades. Excipients are customized for specific dosage forms, functionalities, manufacturing methods, and release rates, and the resulting range of possible excipients can be bewildering for manufacturers trying to develop a formulation or for regulators trying to evaluate a regulatory filing for quality. One example is the development of coated tablets with different release rates, where each type of release may require a different type of coating agent. Another example of potentially confusing grade selection is the excipient hydroxypropyl cellulose (HPC) made by NISSO, which comes in the following grades: H, L, M, SL, or SSL, where each grade has different degrees of substitution and molecular weights. Some of these grades can be used as a suspending agent and other grades can be used as binders for wet or dry granulation.

In Fig. 1, selections for formulation of a capsule are shown based on using the excipient microcrystalline cellulose (MCC) as a dry binder. The figure shows the complexity of utilizing failure modes and risk profiles to assess excipient risk for different combinations.

Information technology offers a powerful tool for the complex, information-intensive tasks involved in the selection of excipients to use in a formulation. Decision support systems are designed to help users make decisions about problems that are not easily specified in advance and where applicable choices and data at a given point in the decision process are changing as selections continue to be made.

The points in the decision process where users need to make a decision are identified as *decision elements*. Throughout this paper, we refer to these points as decision elements, formulation elements, or simply elements. Users select among available options for each element as they created their *decision path*, and the decision path created by a user represents the formulation scenario. Our decision support system allows users to assess formulation scenarios based on risk profiles assigned to the following formulation elements: (1) excipient, (2) dosage form type, (3) excipient functionality, (4) manufacturing method, and (5) excipient grade. Risk assessment profile data are accessed and evaluated by the decision support system for each element, and the calculated risk profile is specific to the combination of the selected elements. In addition, incompatible combinations of excipients and determinant elements are excluded from the decision tree for selection. When all five formulation elements have been selected by a user, the formulation scenario is complete.

A decision support system generally consists of three components:

1. Database of knowledge assembled for the decision elements, where each element is assigned options for users to select from in the decision-making process.
2. Decision processor that manages element selection options and validation of user-created decision paths, and
3. Interactive interfaces that guide users through the selection process and display risk analysis results about selected elements for exploration.

To support the decision processor, the excipient risk assessment database stores master lists of all formulation elements that are part of the decision process, all relevant

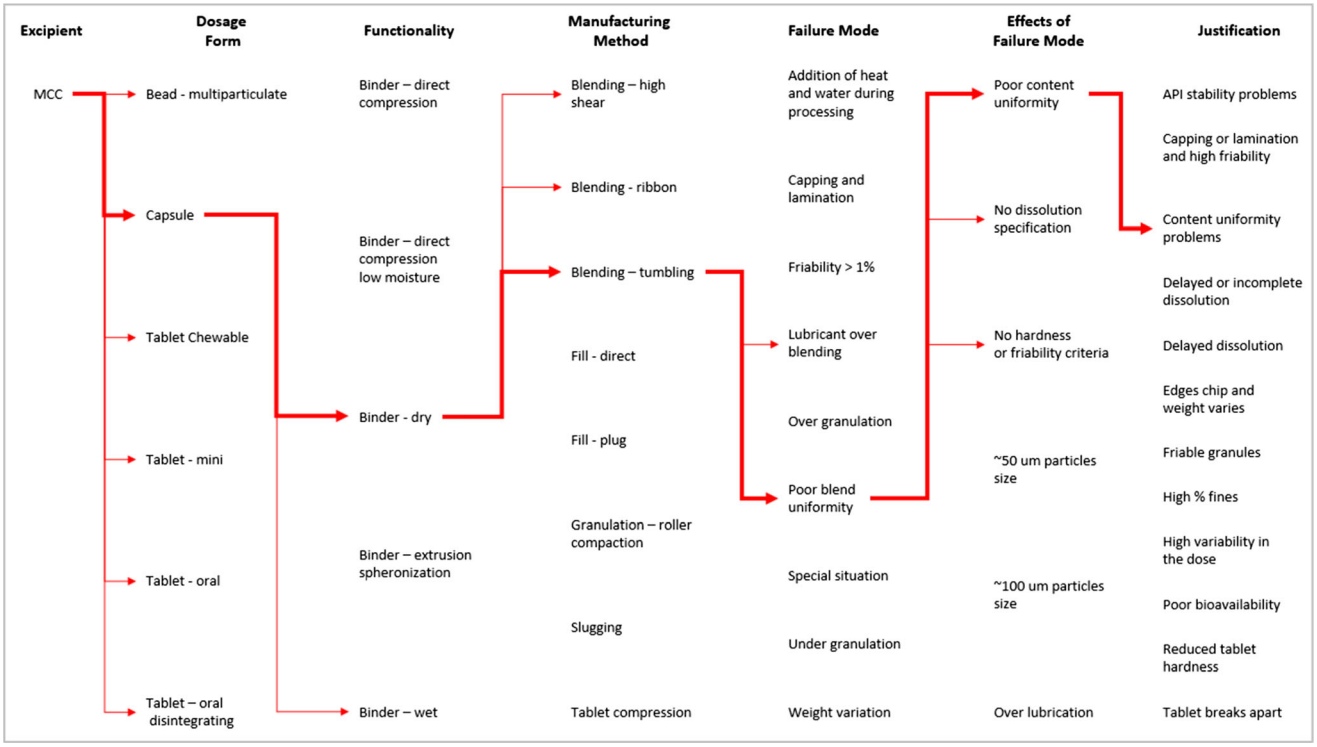


Fig. 1. Failure mode and effect for dosage form and manufacturing method selections using excipient microcrystalline cellulose (MCC) as a dry binder in a formulation

properties of these elements, compatibility rules that define how elements can be combined in a formulation decision path (or formulation scenario), and risk assessment profiles for all valid combinations of formulation elements. Well-constructed decision support systems are adaptable and generally support the contribution of new elements, new properties and new rules without significant changes to the underlying decision engine. As new information becomes available, it can be incorporated easily into the database and the decision management system. Thus, the user has access to a growing body of knowledge that is gathered and presented in a consistent manner.

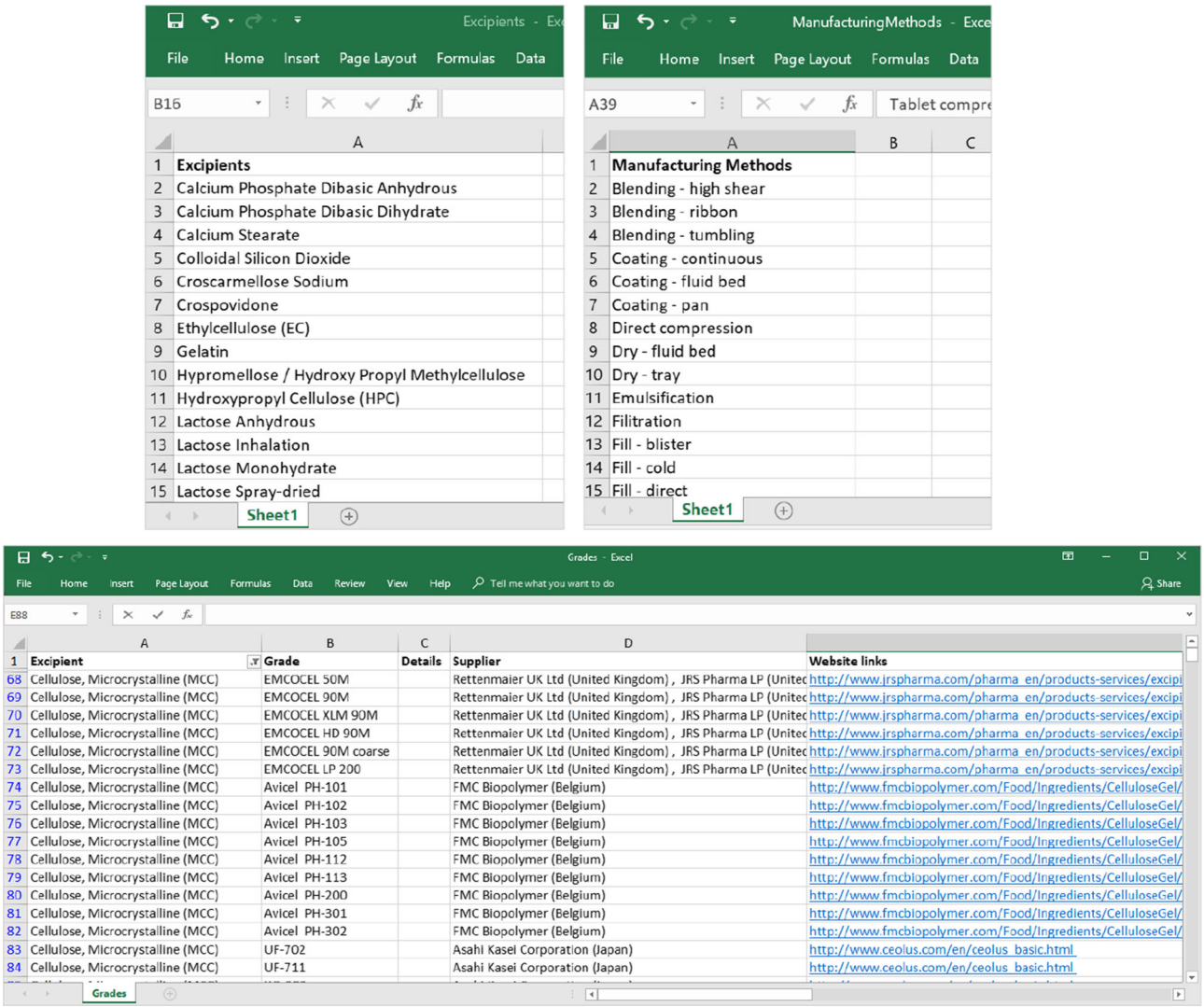
Decision support systems are generally user-friendly and are targeted for non-technical users. For the excipient risk analysis system, building on top of a web-based cyberinfrastructure (6) provides up-front advantages such as user management, access control, and built-in features for data search, exploration, and custom reporting (7,8).

In summary, the thoughtful selection of an excipient requires the formulator to factor in, at a minimum, the dosage form type, excipient functionality, manufacturing method, desired release rate, patient acceptability, patient population, and the compatibility of all selected formulation elements in the formulation scenario. Given the wide range and complexity of choices, decision support offers valuable, user-friendly technology to guide users through their selection process, identifying all possible compatible choices at each decision point and providing continuous feedback for detailed risk assessment as selections are made. To meet this need, we developed a publicly available Excipient Risk Assessment System (ERAS) (9). Our system incorporates data from the excipient physical properties database described in (10). This paper describes the risk assessment database and decision support system. We discuss methods used for data collection and present case studies using ERAS to examine excipient risk in formulation scenarios.

METHODS

The collection of data to populate the database began with the selection of excipients and grades. We chose excipients based upon usage in the pharmaceutical industry and focused on excipients whose risk profiles depend on interactions between grade, dosage form, and manufacturing method. A partial list of excipients in the database is shown in Fig. 2, and the interested reader can go directly to ERAS to see the complete list of excipients (11).

One challenge in identifying excipient types for a database is that excipients have complex structures and among different user groups, can have different names. Excipient types are generally based on their chemistry. For example, the United States Pharmacopeia/National Formulary (USP/NF) defines microcrystalline cellulose NF (MCC) in the following way: “Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.” This definition is based on the chemistry and processing methods that produce the chemical structure of MCC. When MCC is purchased, however, it comes in many different grades based on varying particle sizes, bulk densities, and moisture contents. Different manufacturers have different names and slightly different properties for different excipient grades. These variations made it challenging to assign unique names to the excipients. However, since a grade must be factored into the assessment of risk, it was necessary



	A
1	Excipients
2	Calcium Phosphate Dibasic Anhydrous
3	Calcium Phosphate Dibasic Dihydrate
4	Calcium Stearate
5	Colloidal Silicon Dioxide
6	Croscarmellose Sodium
7	Crospovidone
8	Ethylcellulose (EC)
9	Gelatin
10	Hypromellose / Hydroxy Propyl Methylcellulose
11	Hydroxypropyl Cellulose (HPC)
12	Lactose Anhydrous
13	Lactose Inhalation
14	Lactose Monohydrate
15	Lactose Spray-dried

	A
1	Manufacturing Methods
2	Blending - high shear
3	Blending - ribbon
4	Blending - tumbling
5	Coating - continuous
6	Coating - fluid bed
7	Coating - pan
8	Direct compression
9	Dry - fluid bed
10	Dry - tray
11	Emulsification
12	Filtration
13	Fill - blister
14	Fill - cold
15	Fill - direct

	A	B	C	D
1	Excipient	Grade	Details	Supplier
68	Cellulose, Microcrystalline (MCC)	EMCOCEL 50M		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
69	Cellulose, Microcrystalline (MCC)	EMCOCEL 90M		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
70	Cellulose, Microcrystalline (MCC)	EMCOCEL XLM 90M		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
71	Cellulose, Microcrystalline (MCC)	EMCOCEL HD 90M		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
72	Cellulose, Microcrystalline (MCC)	EMCOCEL 90M coarse		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
73	Cellulose, Microcrystalline (MCC)	EMCOCEL LP 200		Rettenmaier UK Ltd (United Kingdom) , JRS Pharma LP (Unitec
74	Cellulose, Microcrystalline (MCC)	Avicel PH-101		FMC Biopolymer (Belgium)
75	Cellulose, Microcrystalline (MCC)	Avicel PH-102		FMC Biopolymer (Belgium)
76	Cellulose, Microcrystalline (MCC)	Avicel PH-103		FMC Biopolymer (Belgium)
77	Cellulose, Microcrystalline (MCC)	Avicel PH-105		FMC Biopolymer (Belgium)
78	Cellulose, Microcrystalline (MCC)	Avicel PH-112		FMC Biopolymer (Belgium)
79	Cellulose, Microcrystalline (MCC)	Avicel PH-113		FMC Biopolymer (Belgium)
80	Cellulose, Microcrystalline (MCC)	Avicel PH-200		FMC Biopolymer (Belgium)
81	Cellulose, Microcrystalline (MCC)	Avicel PH-301		FMC Biopolymer (Belgium)
82	Cellulose, Microcrystalline (MCC)	Avicel PH-302		FMC Biopolymer (Belgium)
83	Cellulose, Microcrystalline (MCC)	UF-702		Asahi Kasei Corporation (Japan)
84	Cellulose, Microcrystalline (MCC)	UF-711		Asahi Kasei Corporation (Japan)

Fig. 2. Data collection spreadsheets for excipients, manufacturing methods, and grades in the risk assessment database

to assign unique names so that grades (which are a unique name assigned by the manufacturer) could be selected as part of the decision support process.

To calculate the risk of a particular excipient, ERAS takes into account the following factors:

- Required elements of the formulation scenario, these are the excipient, the dosage form type, the manufacturing method, the excipient functionality, and the excipient grade
- Compatibility among elements of the formulation, for example, which excipients and excipient grades are valid for use with tablet or capsule dosage forms, and which excipient functionalities are valid for specific manufacturing methods such as blending or granulation,
- Detailed risk profiles from the database corresponding to the combination of elements in a formulation scenario.

The method used for assigning risk profiles to combinations of elements in a formulation scenario is fundamental to the assessment of risk and its use in the decision process.

Failure Mode Effects Analysis

Failure Mode Effects Analysis (FMEA) is one of the more common methods to assess risk (12). For any risk analysis, the two most important components of risk (R) include the degree of hazard or potential loss (L) and the probability or likelihood of an event occurring (P). In other words, risk is the combination of these two factors; likely events that have a high loss, *i.e.*, cost a lot if occurred, carry the greatest risk, and unlikely events that have a low cost have the least risk. In between these two extremes, the combination of cost and likelihood are combined to give a wide range of risk possibilities. For example, infrequent costly events would be considered low risk because the probability of occurrence is very low, and as the combination of cost and likelihood increases so does the risk.

In FMEA, the likelihood that a given failure mode can be detected (D) is also considered. The FMEA method is used to evaluate the excipient influence on the quality and safety of a drug product. Risk is defined by a risk priority number (RPN) (12,13):

$$\mathrm{RPN} = L \times P \times D \tag{1}$$

Typically, the individual scores for L, P, and D are assigned integer values from 1 to 6 or 1 to 5 (see Table I for coding description), from which the total risk score, *i.e.*, RPN, can be calculated using:

$$\mathrm{RPN} = \begin{pmatrix} 6 \\ 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{pmatrix} \times \begin{pmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{pmatrix} \times \begin{pmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \end{pmatrix} \tag{2}$$

To determine the RPN, the failure mode values must be determined. This is typically done by an expert, that is, someone who has already encountered the failure. Then, using the categories shown in Table I and the assigned values for L, P, and D, the RPN is calculated using Eq. 1. The highest value is 180, the lowest value is 1, and the risk scores are ranked from high to low. Low values are acceptable, moderate values need to be monitored for the failure mode, and high-risk scores need to have mitigation plans.

Typically, FMEA is the first step in a risk evaluation strategy; the goal of the FMEA analysis is to identify the parameters that are most likely to affect product quality. To confirm these findings, which are based upon a subjective evaluation, the FMEA should be followed by an evaluation of the effect of these parameters product performance using statistical methods such as a Design of Experiments (DOE). When actual risk has been determined, a monitoring and mitigation strategy should be developed. This process is described by Kona *et al.* (1–3) and in guidelines Q8, Q9, and Q10 from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (14).

Table I. To calculate the RPN, first the individual components of RPN, the loss (*L*), probability (*P*), and detectability (*D*) need to be assigned values. The ranking assessment of loss (*L*), probability (*P*), and detectability (*D*) we used are given below and are based upon typical coding schemes commonly used in the literature (12,13)

Numerical Rating	Meaning
Hazzard or loss (*L*)	
1	No relevant effect on reliability or safety
2	Very minor, no damage, no injuries, only results in a maintenance action
3	Minor, low damage, light injuries
4	Moderate, moderate damage, injuries possible
5	Critical (causes a loss of primary function; loss of all safety margins, one failure away from a catastrophe, severe damage, severe injuries, max one possible death)
6	Catastrophic (product becomes inoperative; the failure may result in completely unsafe operation and possibly multiple deaths)
Probably of occurrence (*P*)	
1	Highly unlikely (virtually impossible or no known occurrences on similar products)
2	Remote (relatively few failures)
3	Occasional (occasional failures)
4	Reasonably possible (repeated failures)
5	Frequent (failure is almost inevitable)
Detectability (*D*)	
1	Certain—fault will be caught on test
2	Almost certain
3	High
4	Moderate
5	Low
6	Fault is undetected by operators or maintainers

Decision Support Systems

The information for each decision element in a decision path is stored in the database, and a structured data approach is used for the representation and correlation of element data. This approach allows each element and its attributes (or properties) to be defined in a tabular representation. Additional non-data attributes are defined to help with uniqueness constraints, which are useful for identification and uniqueness testing during decision support processing.

Each element in a decision path is stored as a table T of dimension $m \times n$, where m is the number of rows in the table, and n is the number of attributes of the table representing data assigned to the elements. Each row corresponds to the records of a unique element entry with its respective attributes. A row is accessed as T_i where $i \in \mathbb{N}$, $1 \le i \le m$. An attribute in a row is accessed as $T_i.a$ where a is the name of the attribute. Names are defined by the excipient experts who populate the database, and names are unique per table. In our design we added the *id* attribute to each table; its value is the same as the row index, that is, $T_i.id = i$. This id helps to correlate compatible elements and will be described further in the "Results and Discussion" section.

The formulation decision path represents the formulation scenario and is an ordered sequence of formulation elements that is created as the user makes selections. The decision elements are, in order of selection: the excipient, the dosage form, the functionality, the manufacturing method, and the grade. Data entries for each of these elements (*i.e.*, all possible selection options for an element) are stored in database tables: E (excipients), D (dosage forms), F (functionalities), M (manufacturing methods), and G (grades). Each row in an element table, namely, each selection option for that element, is assigned a unique id. Figure 2 shows the data collection spreadsheets used to populate the ERAS database tables for excipients, manufacturing methods, and grades.

Each element table has its own attributes, which are assembled according to (1) formulation data requirements for that element and (2) information that will be displayed to users about that element in the interactive user interfaces. There are unique attributes per table, such as compendial name and chemical name for excipients and the supplier and molecular formula and molecular weight for grades. Additionally, some attribute names are common between tables since they represent the same type of information, such as narrative for the extended description of an element. Table II lists some of the attributes and data for several excipients from the excipient table in the database.

New attributes for formulation elements can be added using new column instructions for the selected formulation

Table II. Selected attributes and data for some excipients from the excipients table in the database

ID	Compendial name	Chemical name	CAS number	Narrative	Submitter
4	Cellulose, microcrystalline (MCC)	Microcrystalline cellulose	9004-34-6	MCC is a white tasteless powder made by the depolymerized cellulose made from the acid treatment of paper pulp…	Stephen Hoag
9	Maltodextrin	Maltodextrin	9050-36-6	Maltodextrin is a non-sweet white powder, nutritive saccharide mixture of polymers that consists…	Stephen Hoag
10	Mannitol	D-Mannitol	69-65-8	Mannitol is a sweet white crystalline powder that is a sugar alcohol isomeric with sorbitol…	Stephen Hoag
11	Croscarmellose sodium	Cellulose, carboxymethyl ether, sodium salt, crosslinked	74811-65-7	Croscarmellose sodium is the sodium salt of a cross-linked, partly O-(carboxymethylated)…	Stephen Hoag
12	Sodium starch glycolate	Sodium carboxymethyl starch	9063-38-1	Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a cross-linked…	Stephen Hoag
13	Pregelatinized starch	Pregelatinized starch	9005-25-8	Starch that has been chemically and/or mechanically processed to rupture all or part of…	Stephen Hoag

element table, this means the information stored in the database can easily be expanded as needed.

Master Lists

A key aspect of ERAS is the correlation of compatibility between selected formulation elements in the formulation scenario. Users create their own scenario by making selections for all formulation elements, but the system must consistently maintain the correctness of the full decision path (all selection already made) with each new element selection. This validation task is performed by accessing the database tables that define compatibility between elements. These tables are the master lists.

The master list tables store the ids of compatible elements in a formulation scenario. A total of ten master lists are defined: *ED* (excipient-dosage form), *EF* (excipient-functionality), *EM* (excipient-manufacturing method), *EG* (excipient-grade), *FD* (functionality-dosage form), *MD* (manufacturing method-dosage form), *GD* (grade-dosage form), *MF* (manufacturing method-functionality), *GF* (grade-functionality), and *GM* (grade-manufacturing method). There are three columns for each compatibility master list: the table id, the id of the first element, and the id of the second element. Entries in the master lists cannot be empty. An entry in a master list implies that both referenced elements are compatible, which means that selecting them simultaneously for a formulation scenario is valid.

Figure 3 shows examples of data collection spreadsheets for defining compatibility between some of the formulation elements: grades and functionality (GF master list), manufacturing methods and dosage forms (MD master list), and grades and manufacturing methods (GM master list). Data for compatibility entries in the master lists are collected by authorized experts registered as contributors for the excipient risk database.

When a new formulation element is selected, the validation of a formulation scenario is based on the availability of compatible elements to select for the next step in the path. Let R be the set of compatible element ids so far at any step of the decision path, let $R' = Compatible(R, S)$ be the new set of compatible elements consisting of elements in R and the selected element S in the next step. The compatible function checks the existence of entries in the last checked master list of ids of the form$(R.\,id, S.\,id)$. If $R' \neq \emptyset$, then there exist compatible formulation elements to continue building the decision path and therefore the formulation scenario is still valid. Otherwise, due to the lack of compatible elements for the current selections, the formulation scenario is invalid. The system begins constructing $R = \{E_i.\,id, 1 \leq i \leq m\}$ where m is the number of rows in the excipients table, which is the number of excipients registered in the database. For each selection, the system checks that R is not empty, and in this case, $R = R'$, that is, the new set of compatible elements is used for the next selection in the decision path. The validation process finishes when S corresponds to a grade selection since this is the final formulation element selected for a formulation scenario.

Master lists data are collected and contributed by excipient and formulation experts. Collection is a manual effort since master list content is based on expert knowledge.

Collection of User Feedback

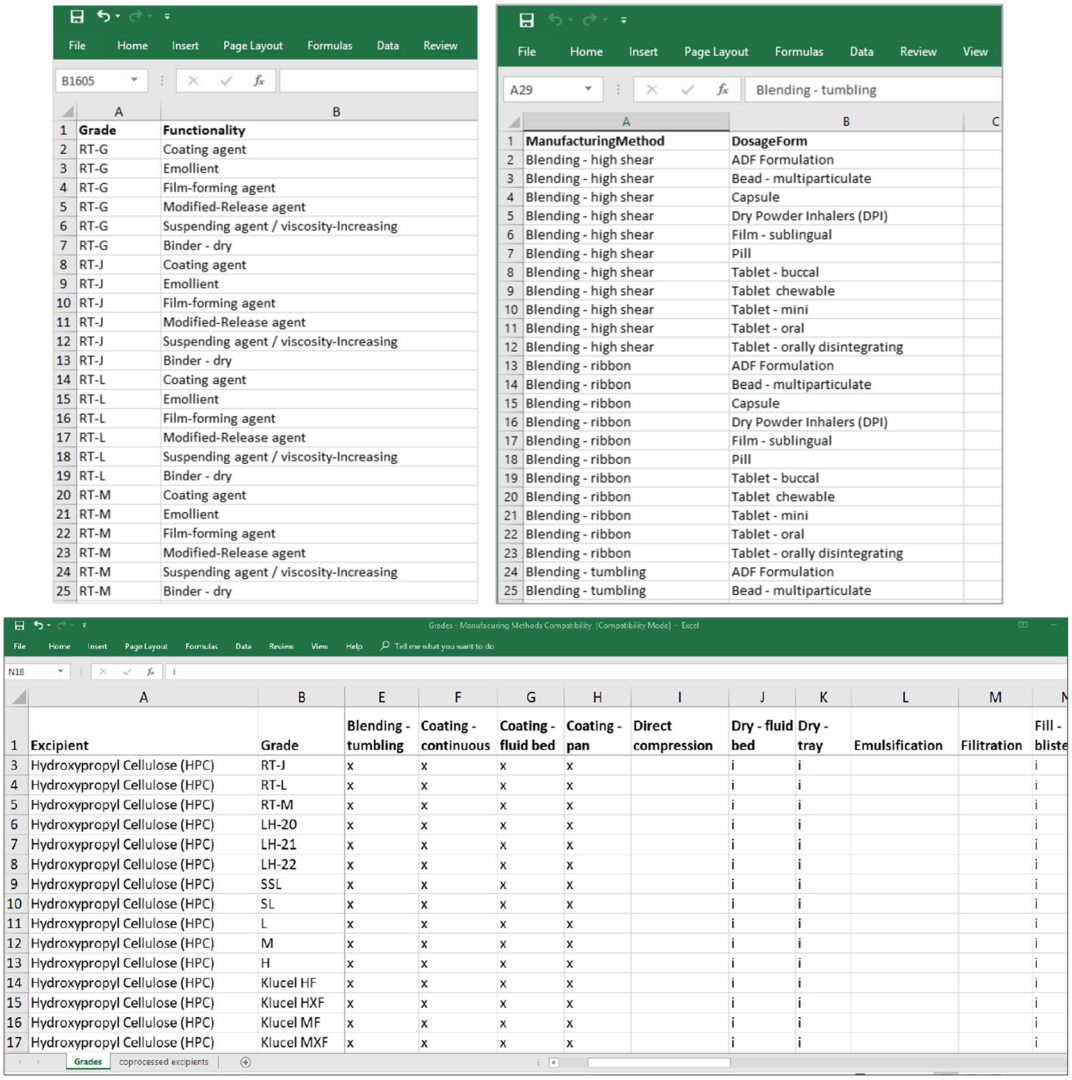
To help the ERAS grow and benefit from the user's experience, there is a section where registered users can provide feedback, suggest updates to the decision rules, and suggest new features for the ERAS. This feedback section can be found at: https://pharmahub.org/wishlist.

RESULTS AND DISCUSSION

In this section, we first describe the data processing and system architecture that underlies ERAS decision support and then discuss the main features and user interfaces. We conclude by working through several case studies that illustrate the value and usability of ERAS.

DATA PROCESSING FOR DECISION SUPPORT

Support for the collection, transformation, and use of data in ERAS decision processing is based on three stages for



	A	B
1	Grade	Functionality
2	RT-G	Coating agent
3	RT-G	Emollient
4	RT-G	Film-forming agent
5	RT-G	Modified-Release agent
6	RT-G	Suspending agent / viscosity-Increasing
7	RT-G	Binder - dry
8	RT-J	Coating agent
9	RT-J	Emollient
10	RT-J	Film-forming agent
11	RT-J	Modified-Release agent
12	RT-J	Suspending agent / viscosity-Increasing
13	RT-J	Binder - dry
14	RT-L	Coating agent
15	RT-L	Emollient
16	RT-L	Film-forming agent
17	RT-L	Modified-Release agent
18	RT-L	Suspending agent / viscosity-Increasing
19	RT-L	Binder - dry
20	RT-M	Coating agent
21	RT-M	Emollient
22	RT-M	Film-forming agent
23	RT-M	Modified-Release agent
24	RT-M	Suspending agent / viscosity-Increasing
25	RT-M	Binder - dry

	A	B	C
1	ManufacturingMethod	DosageForm	
2	Blending - high shear	ADF Formulation	
3	Blending - high shear	Bead - multiparticulate	
4	Blending - high shear	Capsule	
5	Blending - high shear	Dry Powder Inhalers (DPI)	
6	Blending - high shear	Film - sublingual	
7	Blending - high shear	Pill	
8	Blending - high shear	Tablet - buccal	
9	Blending - high shear	Tablet chewable	
10	Blending - high shear	Tablet - mini	
11	Blending - high shear	Tablet - oral	
12	Blending - high shear	Tablet - orally disintegrating	
13	Blending - ribbon	ADF Formulation	
14	Blending - ribbon	Bead - multiparticulate	
15	Blending - ribbon	Capsule	
16	Blending - ribbon	Dry Powder Inhalers (DPI)	
17	Blending - ribbon	Film - sublingual	
18	Blending - ribbon	Pill	
19	Blending - ribbon	Tablet - buccal	
20	Blending - ribbon	Tablet chewable	
21	Blending - ribbon	Tablet - mini	
22	Blending - ribbon	Tablet - oral	
23	Blending - ribbon	Tablet - orally disintegrating	
24	Blending - tumbling	ADF Formulation	
25	Blending - tumbling	Bead - multiparticulate	

	A	B	E	F	G	H	I	J	K	L	M	N
1	Excipient	Grade	Blending - tumbling	Coating - continuous	Coating - fluid bed	Coating - pan	Direct compression	Dry - fluid bed	Dry - tray	Emulsification	Filitration	Fill - bliste
3	Hydroxypropyl Cellulose (HPC)	RT-J	x	x	x	x		i	i			i
4	Hydroxypropyl Cellulose (HPC)	RT-L	x	x	x	x		i	i			i
5	Hydroxypropyl Cellulose (HPC)	RT-M	x	x	x	x		i	i			i
6	Hydroxypropyl Cellulose (HPC)	LH-20	x	x	x	x		i	i			i
7	Hydroxypropyl Cellulose (HPC)	LH-21	x	x	x	x		i	i			i
8	Hydroxypropyl Cellulose (HPC)	LH-22	x	x	x	x		i	i			i
9	Hydroxypropyl Cellulose (HPC)	SSL	x	x	x	x		i	i			i
10	Hydroxypropyl Cellulose (HPC)	SL	x	x	x	x		i	i			i
11	Hydroxypropyl Cellulose (HPC)	L	x	x	x	x		i	i			i
12	Hydroxypropyl Cellulose (HPC)	M	x	x	x	x		i	i			i
13	Hydroxypropyl Cellulose (HPC)	H	x	x	x	x		i	i			i
14	Hydroxypropyl Cellulose (HPC)	Klucel HF	x	x	x	x		i	i			i
15	Hydroxypropyl Cellulose (HPC)	Klucel HXF	x	x	x	x		i	i			i
16	Hydroxypropyl Cellulose (HPC)	Klucel MF	x	x	x	x		i	i			i
17	Hydroxypropyl Cellulose (HPC)	Klucel MXF	x	x	x	x		i	i			i

Fig. 3. Data spreadsheets used by excipient and formulation experts to collect and contribute compatibility data for (1) grades—functionality, (2) manufacturing methods—dosage forms, and (3) excipients—grades—manufacturing methods

the information that defines formulation elements and their risk profiles:

1. *Data collection*—Collected data consists of (1) the names and properties of the elements in a formulation scenario: excipients, dosage forms, excipient functionality, manufacturing methods, and excipient grades, (2) the master lists describing formulation element compatibility, and (3) risk assessment profiles for combinations of formulation elements, where risk analysis data has been determined using the FMEA method. All collected data are stored in traditional spreadsheets according to a standardized format.
2. *Data representation*—Data is processed from the spreadsheets to ERAS database tables. Each decision element is represented in normal form (15) to support unique identification and compatibility verification with other decision elements each time a user makes a new selection in the formulation scenario.
3. *Data exploration*—nformation from elements selected by the user in the formulation scenario is crossed in real time with all compatible elements available for all possible future selections for the scenario. Custom risk assessment reports are continually updated and displayed as selections are made, to enable ongoing user evaluation of risk assessment data and to help users navigate further along the decision path. Interactive, user-friendly interfaces are available to view, search, filter, and sort all data in the database for the formation elements and their risk profiles.

Data Collection

The main body of decision support information was defined, classified, and recorded using Excel spreadsheets. Initial requirements for the data and their use in decision support were identified as the nature of the data and relationships among the data were analyzed. This stage required the collaboration of database designers, system engineers, and experts in formulation and excipient performance to identify and classify the available data and then

determine how it should be represented and used. The resulting design encompasses the following data:

- Elements to consider for the formulation scenarios, and the number and names of each element to include in the database: 30 excipients, 19 dosage forms, 55 functionalities, 21 manufacturing methods, and 454 grades
- Compatibility between the elements at each step of the selection process. Relationships between elements were recorded in master lists, where a compatibility mapping was recorded for each valid pair of element names taken from different element lists, for example (Povidone, Binder-wet) is a valid (excipient, functionality). Ten master lists were built and populated.
- Risk profiles per element and per completed formulation scenario, for example, a risk profile is assigned to this valid combination of formulation elements:

Microcrystalline Cellulose/Tablet-oral/Binder-wet/Blending-ribbon/Avicel PH-101

- Detailed risk assessment results generated by the decision support system based on the formulation elements selected by the user. There is likely to be more than one failure mode for a formulation, and the risk assessment report presents all possible failure modes for the combination of formulation elements in the formulation scenario. For each failure mode, the report identifies:

- Effects of the failure mode
- RPN assigned to the failure mode
- Risk values (determined by excipient and formulation experts) for severity of loss (L), probability of occurrence (P), and detectability (D) used to compute the RPN
- Justification for the values of L, P, and D
- RPN rank (low, moderate, high) based on a pre-set classification across the range of all possible RPN values.

Data Representation

The representation of decision support data and rules needs to be suitable for database queries and determination of interactive, real-time results. The excipient risk assessment database was designed using a structured data approach. Collected data are stored in tabular database tables, which are processed into the database from spreadsheets and assigned unique identifiers for each element record. The master lists used for representing compatibility between elements are also stored as database tables, where lists of relationships use only the identifiers of compatible elements. In this way, the system can effectively and efficiently identify which elements are subsequently available for user selection any time a new selection is made along the decision path. Furthermore, this representation improves search operations by reducing the amount of new data crossing to the currently selected data. In case of incompatibility (or lack of complete database information about selected formulation elements), the system prevents further selections and stores the incomplete sequence into a log. Figure 4 shows a diagram representing the structured data used by the system for compatibility of formulation elements constructed from the master lists.

Data Exploration

Decision support and data exploration interfaces are presented to users from a web-based platform accessible through a browser. The decision support system follows a client-server software design common for this kind of interactive system. The user interface is coded as a plugin using HTML, CSS, and JavaScript. The platform web page offers users access to (1) the decision support system for selecting elements and assembling a formulation scenario, (2) a custom report area displaying risk assessment results, (3) links to search and explore all elements included in the database along with their attributes and their compatibility data, (4) excipient grade validation, which identifies the excipient grades that are still valid for selection at any point in the building of the formulation scenario, and (5) viewers to explore excipient properties and other data.

ERAS is modeled as a web application software. Figure 5 presents an architecture diagram of the system, with software components grouped as abstracted during implementation. The system is composed of two principal components:

1. Data platform: The platform consists of the data management and decision support software. The risk assessment system is built on top of HUBzero™ (6), a content management system for research and education. The knowledge base stores the data required for the system to operate, encompassing data tables, master lists, decision variables and rules, path validation, FMEA structure, RPN values, and additional support data. The software components built on the knowledge base layer correspond to functionalities for data management, decision support (data representations, validation, and results interpretation), and data views (data descriptions and exploration). The data platform component runs on the server side of the application, which is developed as a LAMP system (Linux, Apache, MySQL, and PHP).
2. User interface: Interactive interfaces correspond to the software side visible to users through a web browser. The interfaces allow users to interact with the system using operations and features for creating formulation scenario and visualizing data. “Data Load” functionalities are provided by client-side utilities of the data platform for uploading spreadsheets with formulation knowledge. “Decision Making” is a web interface that loads the information from the server and updates its view as the user makes selections—for every user action there is an automatic response by the system which either enables the next selections or displays a warning message indicating mismatches or lack of sufficient data. “Risk Discovery” corresponds to a set of data views, which are searchable tabular presentations of the risk assessment data. At any time in the decision process, users can explore the results and download them. Data is downloaded as CSV format spreadsheets, a standard format for tabular data.

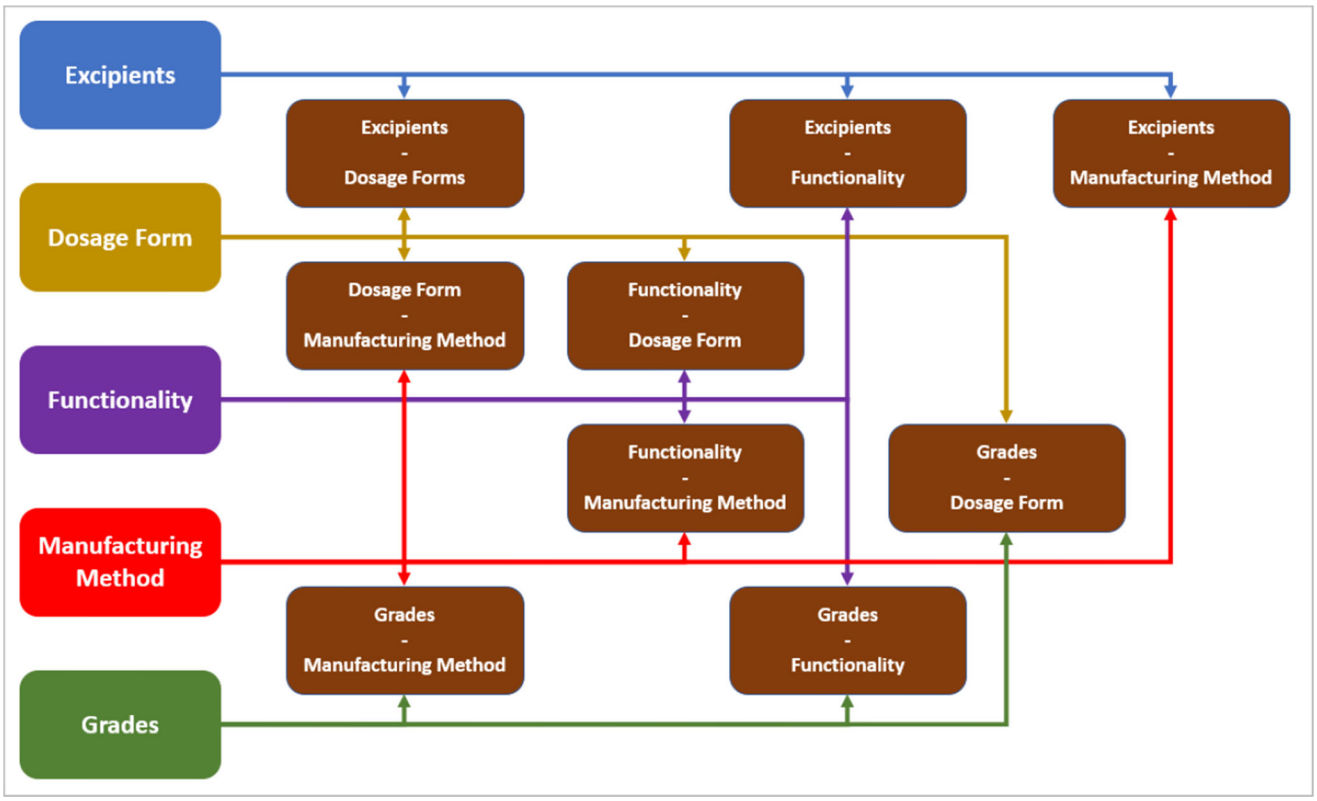


Fig. 4. Diagram of the formulation elements and compatibility relationships described by the master lists

USER INTERFACES FOR DECISION-MAKING

Figure 6 shows the main web page of the ERAS system. In the decision support area, decision elements are enabled as users make selections for their formulation scenario, and the risk assessment results are updated with each selection. Excipient grades that continue to be valid based on the selected elements are available for review. Users can access the raw information for the elements (*e.g.*, attributes and compatibility) using the Explore Options area. Additional database data can be accessed using the Other Data area; this includes all risk assessment information available in the system, property measurements for the excipients, list of suppliers, and notifications generated by ERAS.

The principal feature of ERAS is the interactive user interface where users select elements to create a formulation scenario based on the underlying decision engine that processes database information about elements as users make selections.

Users select an excipient first and then select a dosage form. After an excipient has been selected, only dosage forms compatible with that excipient will be available for selection. A branching in the decision path occurs after the selection of the dosage form. Users can select the excipient functionality followed by a manufacturing method or they can select a manufacturing method first, followed by the excipient functionality. Finally, the excipient grade is selected, and the formulation scenario is complete.

Because the selections are stored as structured data, the system always returns compatible choices for the elements at every decision point. For each selection, the system takes identifiers for all currently selected elements and verifies which elements for the next step are compatible. This guarantees that users are making valid selections. It also supports the display of detailed risk assessments in the risk report at each selection step, even when the formulation scenario is incomplete. As an example, before the grade element has been selected, the risk report will present detailed risk assessment data for *every grade that is compatible* with the user's currently selected formulation elements (excipient, dosage form, functionality, and manufacturing). Risk assessment values are listed for all possible compatible scenarios, allowing users to "jump ahead" to explore what the results of any possible next selections would be.

ERAS offers many user-friendly features for guiding users through the selection process and exploring risk assessment results. In the Select Options area, the user starts by clicking the Excipient button at the left side of the graph to open a menu listing all available excipients currently stored in the database. After a selection is made, the button changes color to show that this element has been chosen. Additionally, the sequence of selected element choices is displayed above the selection buttons, and each displayed formulation element links to a view with additional information for that element.

After each selection, the button for the next step in building the formulation scenario is enabled. As with the excipients button, each enabled button opens a menu with the list of available choices for that element. Choices depend on compatibility with the set of selections already made in the scenario. For example, you would not use a wet granulation binder when doing dry granulation or roller compaction; thus, materials that can only be used as wet granulation binder would be excluded from the possible selections. Note, if the

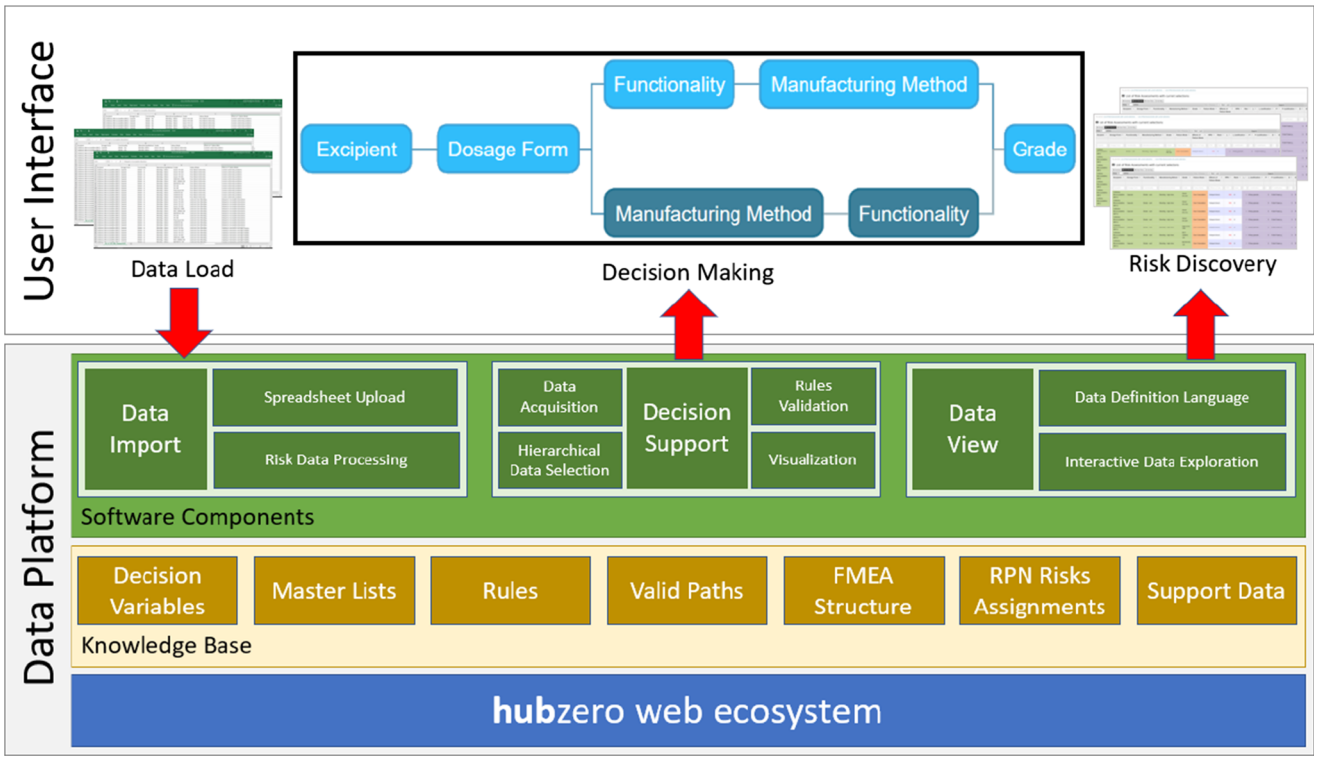


Fig. 5. ERAS software architecture diagram

binder could be used in wet or dry granulation then this binder section would not be excluded.

A completed formulation scenario is represented by the sequence of elements selected by the user from Excipient though valid grade, Fig. 7 shows a completed scenario with the following selections:

- Excipient: *Cellulose Microcrystalline (MCC)*
- Dosage Form: *Tablet–oral*
- Functionality: *Binder–dry*
- Manufacturing Method: *Blending–ribbon*
- Grade: *Avicel PH-101*

Changes in the formulation scenario can be made by clicking the button where a change is required. If the button indicates that a selection has already been made, then a warning message notifies the user that subsequent elements in

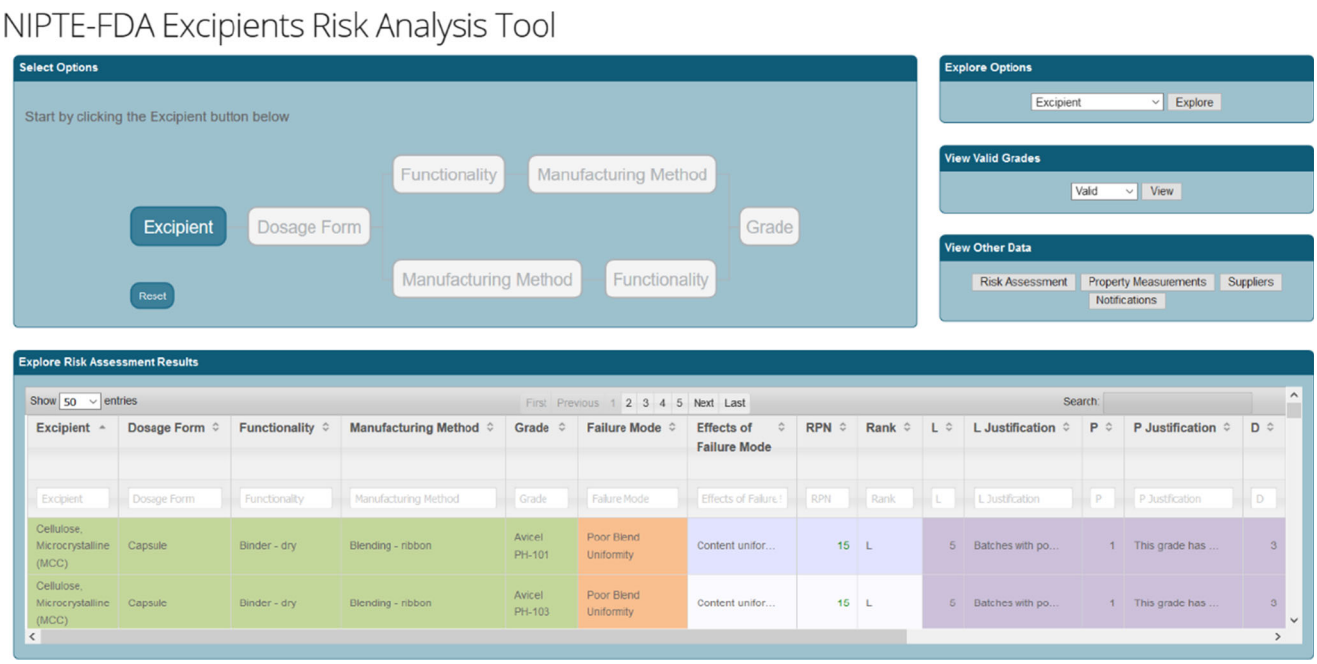


Fig. 6. Excipient Risk Assessment System user interface for creating and analyzing formulation scenarios

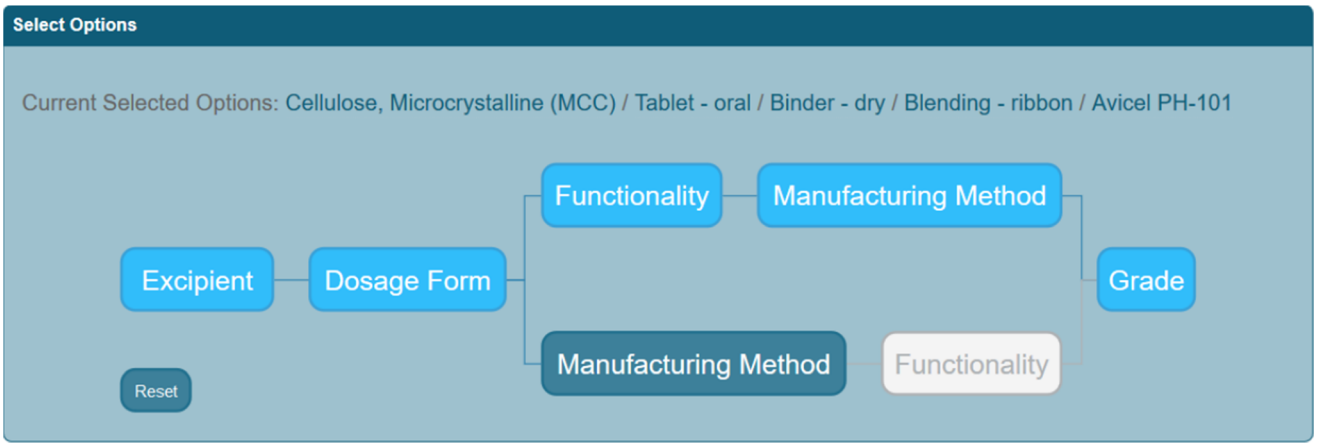


Fig. 7. Example of a completed decision path

the scenario might not be compatible and therefore will be removed from the existing scenario. In this way, a valid formulation scenario is guaranteed, and only valid scenarios are displayed to the user regardless of changes. The entire scenario can be cleared by clicking the reset button.

Results for the user's formulation scenario risk analysis are displayed in a tabular report in the ERAS results area. The results report contains detailed risk data for all valid formulation scenarios reachable according to selections already made. Before any selections are made, the report shows all possible risk results for all combinations of compatible elements currently available in the database. With each element selected by a user, the list narrows to the available, compatible decision elements and their risk results, given current selections in the user's formulation scenario.

Each formulation scenario in the risk report identifies the failure mode, effects of failure mode, the RPN, values used to compute RPN (severity of loss, probability of occurrence, detectability), justifications, RPN rank (low, medium, high), and the name of the contributor of the risk assessment data. Figure 8 shows risk assessment results for the formulation scenario displayed in Fig. 7.

CASE STUDY: THE EFFECT OF MANUFACTURING METHODS ON MCC RISK

To illustrate the complexity of assessing the risk of excipients with multiple failure modes, let us consider MCC, which has numerous grades designed for different manufacturing methods. Different grades used in different manufacturing methods can have different failure modes and hence, different therapeutic efficacy and economic risks for a manufacturing process.

In many references, such as the Handbook of Excipients, MCC is considered a tablet and capsule diluent or filler binder (16,17). To conduct a comprehensive risk analysis, however, the way MCC is used in a formulation also needs to be considered. Thus, in the ERAS database, we divide the filler-binder category into several subgroups, such as a wet binder, dry binder, and direct compression binder among others. In general, MCC is considered one of the most compactible materials that can be used by formulators, but MCC does not flow well as compared to other fillers because it has low bulk density. For this case study, we will examine how ERAS can help assess risks for different manufacturing methods based on risk profiles built into the database for MCC when used as a direct compression binder.

To assess excipient risk, ERAS guides a user through a sequence of choices to describe the formulation. After each selection, ERAS uses information in the database to identify all possible choices for the next decision point in the sequence and displays them in the pull-down menu. At the same time, the system eliminates all choices that are incompatible with previous selections; these choices cannot be seen and are not available for selection. For example, if the user selects direct compression for the manufacturing method in the formulation scenario, ERAS eliminates all future choices related to risks associated with wet granulation and drying. The user's selections for the sequence of decision points are analyzed by ERAS to determine the risk of the formulation scenario.

The first step in the decision process is the selection of an excipient, and we choose MCC. The dosage form is selected next because the failure mode depends on excipient functionality, and the role an excipient plays depends on the type of dosage form. ERAS lists several dosage form choices for which MCC can act as a direction compression binder, such as chewable tablets, multiparticulate beads, capsules, mini-tablets, and orally disintegrating tablets, as well as the standard oral tablet. We choose the standard oral tablet. MCC is a very versatile excipient that can be used in many types of manufacturing processes, and ERAS can be used to assess how one excipient can have many different failure modes. Our case study illustrates very common uses of MCC and presents valuable risk information for the formulation scenarios described here.

The reason the type of dosage form needs to be selected early in the decision process is because the choices for excipient functionality and manufacturing method, as well as the resulting failure modes, depend on the type of dosage form. For example, failure modes for using MCC as a binder in a chewable tablet (which needs to fall apart in the mouth) will be different from failure modes for traditional oral tablets (which typically release API in the small intestine). Thus, to be able to evaluate failure modes and their risks, users need to account for the functionality (or role) of MCC for the

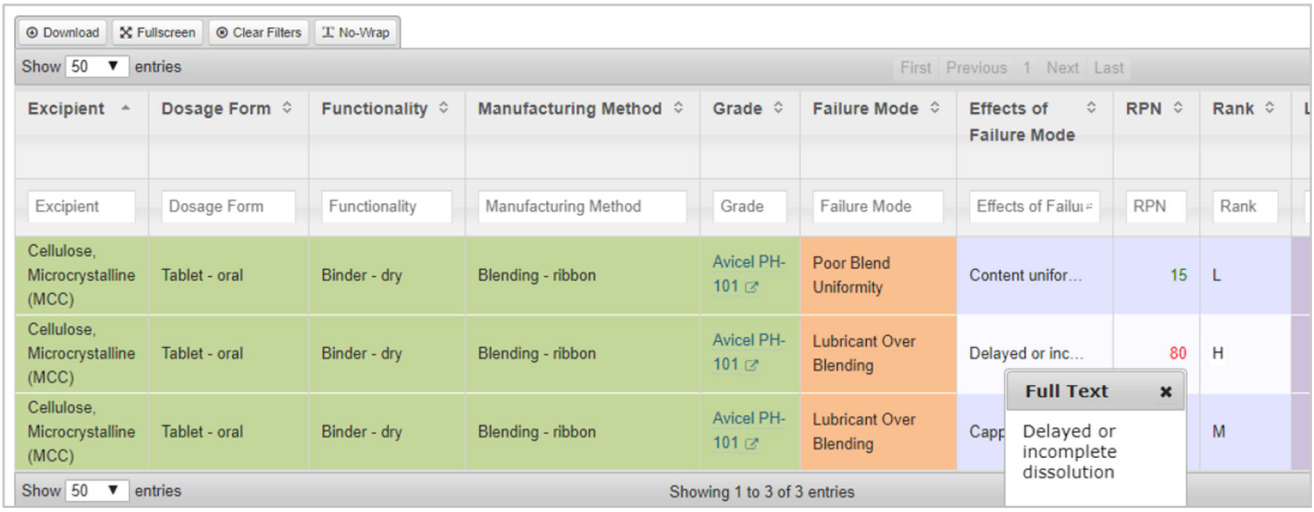


Fig. 8. Risk assessment results for the formulation scenario represented in Fig. 7, the partial display shows the failure modes, their effect, the RPN value and RPN. Not shown columns are the *L*, *P*, *D* values and their respective justifications

selected dosage form, given the requirements for performance. With ERAS, users can easily run through alternate formulation scenarios using MCC for the selected dosage form and functionality to review the reported failure modes and assess the risks. There are many processing strategies and unit operations that can be selected for manufacturing a tablet. ERAS includes direct compression, blending, filling, wet granulation, roller compaction granulation, and slugging. Forty MCC grades are available for users to choose from. Recall that excipient grades are optimized to overcome various problems associated with a particular manufacturing method, and the risks associated with each selected combination of manufacturing method and grade can be evaluated using ERAS.

After the dosage form type and functionality for MCC are selected, users choose a manufacturing method. We select direct compression. When evaluating the use of MCC in direct compression, there are several failure modes that can impact dosage form performance. For example, if the formulation does not flow well, the resulting failure mode is weight variation, which impacts patients as dosing variation and poor content uniformity. Another failure mode is poor mechanical strength, with reported failure effects of friability, capping, or low hardness. Another key failure mode of MCC (a plastic material) is sensitivity to lubricant over-blending. This can be problematic depending on API and batch size. Finally, if the tablet is over compressed and low dose, there can be delayed dissolution—a low porosity failure. Even though MCC is a hydrophilic excipient when used in high-concentrations, low-dose drugs that are poorly soluble have a risk of delayed dissolution. The ERAS can be used to identify and explore these failure modes, the effects of the failure, and the predicted risk for this scenario. Users can then assess the risks and review their RPN component justifications; with this information formulators can take corrective action to mitigate the risk as such as adding a disintegrant.

To see how users can review the failure modes and risk assessment results presented by ERAS, let us look at the risk assessment for our formulation scenario:

- Excipient: *Cellulose Microcrystalline (MCC)*
- Dosage Form: *Tablet–oral*
- Functionality: *Binder–direct compression*
- Manufacturing Method: *Direct compression*

The system reports the most likely failure modes and the consequences or effects of each failure mode. In addition, the system predicts the RPN and breaks it down into its three components so users can see how the RPN was computed. Numerical values and justifications are given for severity of loss (*L*), probability (*P*), and detectability (*D*).

Let us explore the ERAS report on risk assessment results for this formulation scenario (Fig. 9). Filtering on the report's grade column for Avicel PH-101 (small particle size), we find that the RPN for friability is 10, which is low and what you would expect for a typical direct compression formulation. For the purposes of the ERAS, a typical formulation is defined as: API one part, fillers and binders two to three parts, a disintegrant ~ 3 to 5% *w/w* for "super disintegrants," 10 to 20% *w/w* for traditional disintegrant, and a lubricant ~ 0.5 to 1.5% *w/w*; these are the types of formulations that one finds in textbooks that discuss typical formulation methods (16,18). However, judgment should be applied for reported assessments since results represent "typical" formulations. If this were a high-dose formulation with a poorly compressible API that was on the edge of failure, the risk could be substantially higher.

We can also review failure modes involving mechanical properties like capping and lamination. These are higher risk failures than friability, and the RPN reported risk is intrinsically higher because the consequences are more serious. Detection is more difficult as sometimes tablet capping will not be immediately apparent. Tablets may cap in the bottle during shipping—posing a significant detectability issue. Weight variation risk is moderate, again for a typical formation. There could be drug products with serious problems if the API did not flow well. Finally, poor bioavailability is a higher risk as the consequences are serious. When drugs are not absorbed, the patient does not receive the full benefit of the medication. The higher risk is the result of detectability issues in the manufacturing environment. Once the product is used, poor bioavailability is hard to detect unless *in vitro in vivo* correlation or *in vitro*

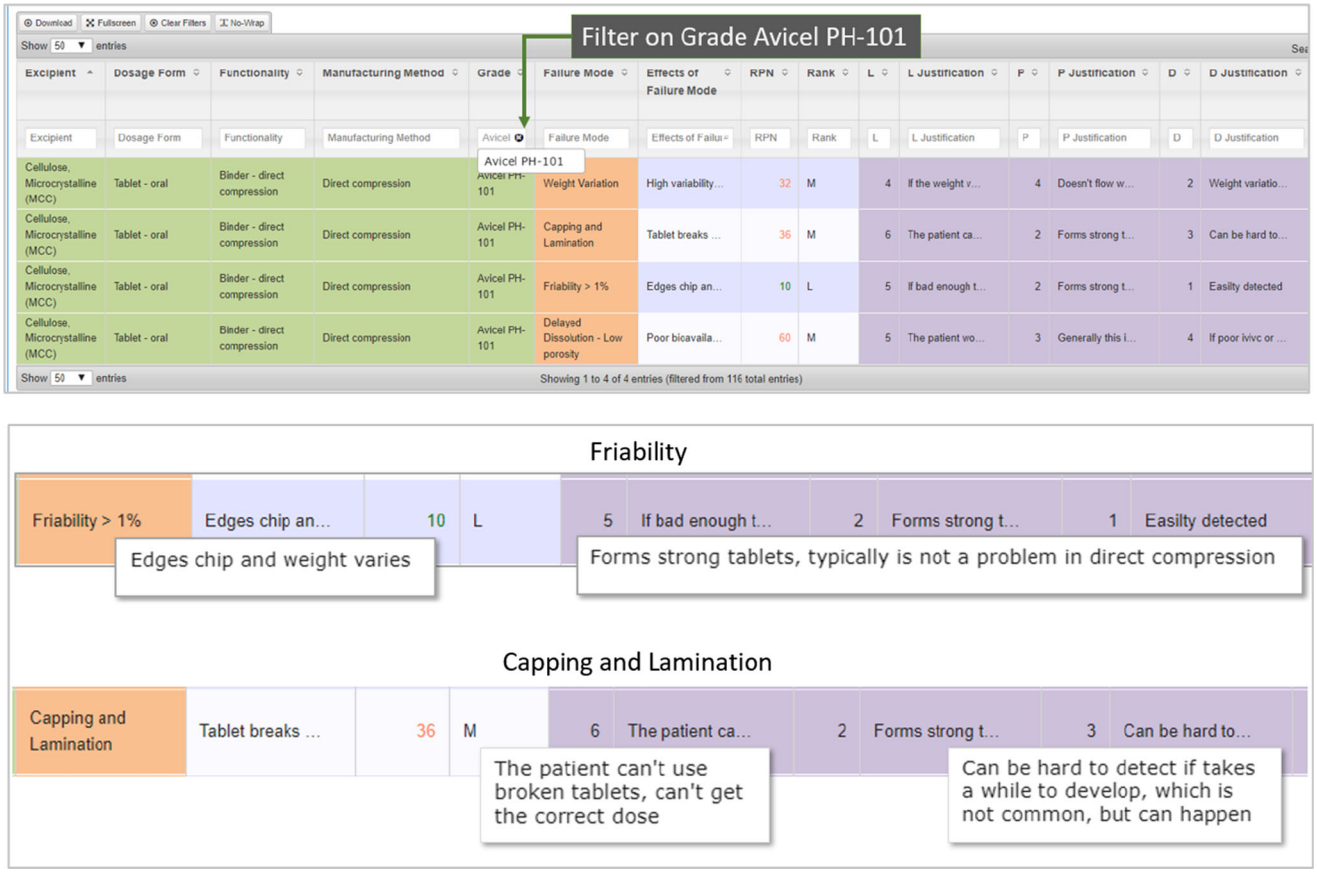


Fig. 9. Failure modes and RPN risk assessment for the formulation scenario: Excipient MCC, Dosage Form Tablet-oral, Functionality Binder-Direct Compression and Manufacturing Method Direct Compression. The user filtered on Grade Avicel PH-101 (top). Risk assessment rows for two of the failure modes, "Friability" and "Capping and Lamination" have been extracted and enlarged, they appear below the viewer (bottom)

in vivo relation IVIVC/IVIVR is available (19). Since this is not typically present, a higher risk is assigned during manufacturing.

Now let us use ERAS to select another formulation scenario for oral tablets and MCC. For high-dose drugs, drugs that are poorly compressible, or drugs that do not flow well, formulators often use a granulation method to engineer particles/granules that have better flow and compressibility. Here again, the issue of excipient grade selection becomes critical, as there are grades developed specifically for different types of granulation (wet, dry, *etc.*). We will use MCC as a dry binder and evaluate different manufacturing methods and their reported risks.

If high shear blending is selected as the manufacturing method with Avicel PH-101 as the selected grade, our system warns that the industry does not typically use high shear blending on dry powders, especially in a formulation scenario with extra granular blending of a lubricant. For this formulation scenario, the warning message in Fig. 10 appears.

Then if tumbling blending is selected—which is a standard practice—the identified failure modes are lubricant over-blending and poor blend uniformity. The ERAS reports that blend uniformity is assigned a moderate risk, with probability of occurrence dependent on grade particle size. As discussed by Oka *et al.* (20), granulations will not segregate unless segregation occurs in the dry blend stage or when preferential wetting of one component by the binder solution or during the wet massing stage leading to an enrichment of API in particles of different sizes, *i.e.*, API concentration is a function of particle size. Thus, if the granulation process is not controlled, there can be content uniformity problems in which the API concentration is a function of particle size. Generally, these problems should have already been addressed during process development, but they could arise during blending if not assessed previously.

For lubricant over blending, there are two possible effects, delayed dissolution and capping or lamination. A medium risk is assigned to capping or lamination, which is usually easy to detect as the failure generally shows up shortly after tableting. But for formulation on the edge, it can show up later when the patient or pharmacist finds a broken or friable tablet as the drug is dispensed. This is problematic as the dose will not be correct for capped products. The final consequence of lubricant over-blending is delayed dissolution. This is assigned a moderate to high risk and needs to be evaluated. Risk is higher when IVIVC/IVIVR are not present because dissolution measures for the standard release test may not detect the problem. ERAS presents failure mode consequences for the typical formulation and the API has not been factored in. Actual risk may vary depending upon API characteristics.

Let us consider another formulation scenario, this time using MCC as a binder (sometimes called a filler/binder) in a wet granulation process. In this scenario, the manufacturing method makes tablets using granules made

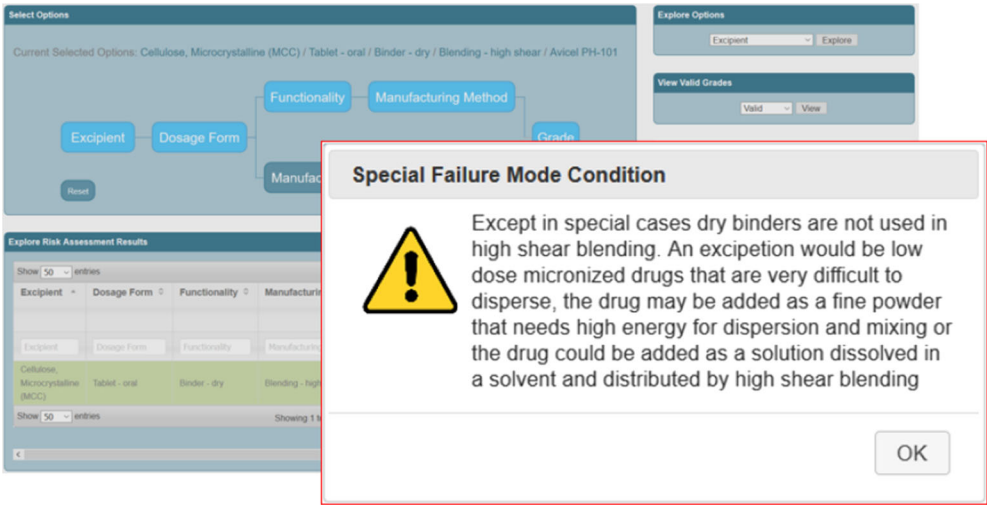


Fig. 10. ERAS reports special warning conditions for non-typical use patterns

via wet granulation. We select these formulation elements for the scenario:

- Excipient: *Cellulose Microcrystalline (MCC)*
- Dosage Form: *Tablet–oral*
- Functionality: *Binder–wet*
- Manufacturing Method: *Tablet compression*

For this formulation, the first two failure modes are over granulation and under granulation, with failure effects of delayed dissolution, reduced tablet hardness, friable granules, and high percentage of fines. These failure modes are high to moderate risk, indicating that the granulation end point must be monitored, that is, the manufacturing process would be more robust if process analytical technology (PAT) system was used and they did not just rely on fixed granulations times. For over granulation, this can lead to delayed dissolution and can reduce tableting hardness. Obviously delayed dissolution is more consequential to the patient, so the assigned risk is higher (see

List of Not Valid Grades with current selections

Download | Fullscreen | Clear Filters | No-Wrap

Show 50 entries

First Previous 1 Next Last

Grade	Excipient	Dosage Form	Functionality
Grade	Excipient	Dosage Form	Functionality
Avicel PH-102	Cellulose, Microcrystalline (MCC)	Bead - multiparticulate Capsule Tablet chewable Tablet - mini Tablet - oral Tablet - orally disintegrating	Binder - direct comp Binder - dry
Avicel PH-103	Cellulose, Microcrystalline (MCC)	Bead - multiparticulate Capsule Tablet chewable Tablet - mini Tablet - oral Tablet - orally disintegrating	Binder - direct comp Binder - dry

Fig. 11. Grade choices no longer valid for the formulation scenario. Partial view of report which shows all grades which can longer be selected for the current formulation scenario. The report shows all dosage form, excipient functionality, and manufacturing method selections that are valid for these grades

discussion above for IVIVC/ IVIVR). Low tablet hardness is more easily detected and thus, less likely to cause problems for the patient but could lead to higher lot failure rates for the manufacturer, so moderate risk is assigned.

For under granulation, the powder is under granulated by not adding enough binder or not mixing long enough. This can lead to a friable granule or a high percentage of fines (either because of friable granules or because the granules were never fully formed). Friable granules can lead to flow problems and poor compressibility, which can cause weight variation. This increases the risk to the patient and is hard to detect without a PAT system. Thus, the friable granules failure was assigned a higher risk. While the high percentage of fines can be problematic, this condition is more easily detected by the particle measurements that are typically done at the end of the granulation process. Thus, it is assigned a moderate risk. The results highlight manufacturing issues and the way the granulation end point is determined. A PAT system that can accurately measure granulation end point and particle size will reduce risk to patients. Therefore, in this case, the risk depends on the equipment used.

The final consequence of failure is API stability (*i.e.*, degradation) caused by addition of heat and water during granulation. Manufacturers can mitigate this failure by minimizing water addition and heat exposure. This risk is drug dependent, and the failure was given a moderate risk because (1) it was assumed that a stability assessment was done and if the drug were unstable another manufacturing method would have been selected, and (2) drug degradation is easily detectable because the FDA requires manufacturers to develop stability-indicating assays for release of their product.

At every decision point in the formulation scenario, ERAS reports which grades are "still valid" and which grades are "no longer valid" as selections for the scenario. For example, in Fig. 11, Avicel PH-102 and Avicel PH-103 are no longer valid for the scenario under discussion. Avicel PH-102, which is considered a direct compression grade, is listed here. While it is possible to use Avicel PH-102 as a wet binder, this is not typically done. MCC loses compressibility during wet granulation and Avicel PH-102 (a less compactible better flowing grade) reduces the compatibility of MCC and increases the flow rate. For this scenario, it is better to use a more compressible grade such as Avicel PH-101. In addition, Fig. 11 lists the low-moisture grade Avicel PH-103 because manufacturers generally do not buy a more expensive low-moisture material and then add water to it.

Comprehensive documentation for ERAS, including user guide, master lists, risk data descriptions, and complete database diagram can be found at https://pharmahub.org/app/site/collections/excipients-risk/webpage/UserGuide_ExcipientsRiskAnalysisTool_12-2018.pdf

CONCLUSION

Excipient selection is critical to formulation design since excipients can profoundly affect pharmaceutical product safety and therapeutic effectiveness. The behavior of excipients is complicated with many different failure modes that depend on dosage form, manufacturing method, excipient functionality, and grade. Assessment of excipient risk and the consequences of failure can be a daunting, data-intensive task due to the large number of possible combinations of formulation elements and the complexity of interrelated excipient behaviors. The ERAS decision support system has been designed to help formulation developers and regulatory agencies analyze excipient failure modes as they interactively create and evaluate formulation scenarios.

ERAS formulation scenarios are created through an interactive decision-making interface where users select excipients, dosage forms, functionality, and manufacturing methods, with guaranteed compatibility among selected formulation elements. The interactive system is supported by three principle components: (1) a database of knowledge assembled for the formulation elements, (2) a decision processor that manages element selection and validation, and (3) interactive interfaces that guide users through the decision-making process and display comprehensive risk assessment results.

The ERAS database assembles and represents data that is rich in quantitative and qualitative information about excipient behavior and the formulation process. It encompasses master lists of formulation elements and their properties, compatibility mappings describing relationships among elements at each step of the decision-making process, and detailed failure mode and risk assessment data for all valid formulation scenarios. ERAS reports assessment results to users in searchable "data views" that display formulation failure modes and their consequences, computed RPN and rank, and determinant risk values with justifications. Given the wide range and complexity of formulation choices, ERAS offers valuable, user-friendly technology to guide users through the formulation decision-making process, with continuous feedback for risk assessment as selections are made.

The science and art of solid oral formation using particulate materials is still an evolving field that lacks first principle models and is often based upon empirical knowledge gained through years of experience. The development of tablet and capsule formulations is a complex undertaking that relies on integrating a broad range of information about excipient grades, dosage forms, manufacturing methods, and other formulation factors to make appropriate choices for the formulation design. We have shown how a decision support system could be used to evaluate the risk of an excipient in a wide variety of formulation and manufacturing scenarios. ERAS offer a knowledge-based solution for organizing and using a large body of collected information and risk assessment data on the many different excipient grades and their functionality.

ACKNOWLEDGMENTS

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REFERENCES

1. Fahmy R, Kona R, Dandu R, Xie W, Claycamp G, Hoag SW. Quality by design I: application of failure mode effect analysis (FMEA) and Plackett-Burman design of experiments in the identification of "main factors" in the formulation and process design space for roller-compacted ciprofloxacin hydrochloride immediate-release tablets. AAPS PharmSciTech. 2012;13(4):1243–54.

2. Claycamp HG, Kona R, Fahmy R, Hoag S. Quality-by-design II: application of quantitative risk analysis to the formulation of ciprofloxacin tablets. AAPS PharmSciTech. 2015:1–12.
3. Kona R, Fahmy R, Claycamp G, Polli J, Martinez M, Hoag S. Quality-by-design III: application of near-infrared spectroscopy to monitor roller compaction in-process and product quality attributes of immediate release tablets. AAPS PharmSciTech. 2014:1–15.
4. Ganesan A, Barakat K. Solubility: a speed–breaker on the drug discovery highway. MOJ Bioequiv Availab. 2017;3(3):56–8.
5. Mitra A, Kesisoglou F. Impaired drug absorption due to high stomach pH: a review of strategies for mitigation of such effect to enable pharmaceutical product development. Mol Pharm. 2013;10(11):3970–9.
6. McLennan M, Kennell R. HUBzero: a platform for dissemination and collaboration in computational science and engineering. Comput. Sci. Eng. 2010;12(2):48–53.
7. Catlin AC, HewaNadungodage C, Fernando S, Bejarano A, Desigavinayagam P, Patil O, editors. Fully integrating data with compute workflows: a platform to better serve scientific research. Gateways: the 13th gateway computing environments conference; 2018.
8. Catlin AC, HewaNadungodage C, Pujol S, Laughery L, Sim C, Puranam A, et al. A cyberplatform for sharing scientific research data at DataCenterHub. Comput. Sci. Eng. 2018;20(3):49–70.
9. NIPTE-FDA Excipients risk analysis tool. [Internet]. 2017. Available from: https://pharmahub.org/excipient-risk-analysis. Accessed 8 Dec 2018
10. Wang T, Alston KM, Wassgren CR, Mockus L, Catlin AC, Fernando SR, et al. The creation of an excipient properties database to support quality by design (QbD) formulation development. Am Pharm Rev. 2013;16(4):16–25.
11. Bejarano A, HewaNadungodage C, Wang F, Catlin A, Hoag S. Decision support for excipient risk assessment in pharmaceutical manufacturing 2018 [Available from: https://pharmahub.org/excipient-risk-analysis. Accessed 8 Dec 2018
12. IPEC. The IPEC Risk Assessment Guide for Pharmaceutical Excipients, Part 1 – Risk Assessment for Excipient Manufacturers 2017 [Available from: https://ipec.org. Accessed 8 Dec 2018
13. Wikipedia. Failure mode and effects analysis. 2019.
14. ICH. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [Available from: https://www.ich.org/home.html. Accessed 8 Dec 2018
15. Codd EF. Further normalization of the data base relational model. In Data Base Systems. In: Rustin R, editor. Courant Computer Science Series. 6. Englewood Cliffs, N.J.: Prentice-Hall; 1972. p. 33–64.
16. Hoag SW, Augsburger LL. Pharmaceutical dosage forms: tablets. 3rd ed. New York: Informa Healthcare; 2008.
17. Sheskey PJ, Cook W, G., Cable CG, editors. Handbook of pharmaceutical excipients. London UK: Pharmaceutical Press; 2017.
18. Augsburger LL, Hoag SWH, editors. Pharmaceutical dosage forms: capsules. Boca Raton: CRC Press; 2018.
19. Food and Drug Administration US. Extended release solid dosage forms: development, evaluation and application of in vitro/in vivo correlations. In: FDA, editor; 1997.
20. Oka S, Smrčka D, Kataria A, Emady H, Muzzio F, Štěpánek F, et al. Analysis of the origins of content non-uniformity in high-shear wet granulation. Int J Pharm. 2017;528(1):578–85.