A Prototype Intelligent Hybrid System for Hard Gelatin Capsule Formulation Development

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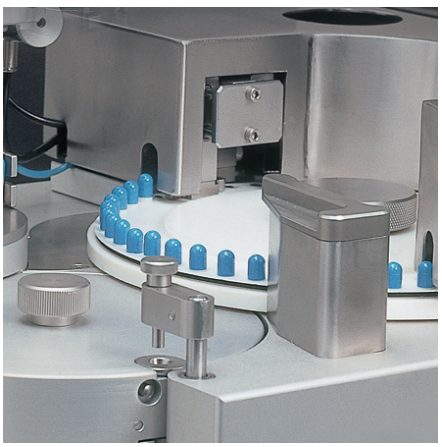

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Although hard gelatin capsules are perceived to be a simple dosage form, the design of formulations for the capsules can present significant challenges. The authors have created a prototype hybrid system by linking a decision module (ES) with a prediction module (ANN) capable of yielding formulations of a model BCS Class II drug.

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Societal pressures to reduce healthcare costs, coupled with the pharmaceutical industry's need to maintain its economic incentive to develop new drugs, have required that the industry increase speed to market and reduce the number of failures and overall cost of new drug development. This need has made it imperative for the industry to use efficient, systematic approaches to both drug discovery and formulation design.

To accelerate drug discovery, scientists now use high-throughput biological screens and combinatorial chemistry that lead to the rapid discovery and identification of numerous potentially useful drugs. Given this high rate of discovery, drug delivery system development for these drug substances—rather than drug discovery itself—is likely to be the rate-limiting step in getting new drugs to market.

Drug substances must be formulated into dosage forms to be practical. These dosage forms must meet the prescribed drug delivery requirements as well as be manufacturable. These requirements present formulation scientists with a complex array of variables. The days of the traditional trial-and-error approach to formulation development based on individual formulators' experiences are gone, and pharmaceutical scientists must adopt efficient, systematic approaches to keep pace with both the numbers and complexity of new therapeutic substances. Indeed, the challenge to drug delivery has grown significantly in recent years as new, more-potent compounds are being developed that often lack the solubility and permeability characteristics needed for effective oral drug delivery.

Capsules occupy a central role in drug development. Because they are perceived to be simpler to manufacture than other oral dosage forms and because of the need to shorten the overall development period, capsules are frequently the first dosage form considered for any orally administered drug, often with the expectation that a compressed tablet will be the final marketed form. Among solid dosage forms, the capsule is second only to the compressed tablet in terms of frequency of use. Given the unique advantages of this dosage form, the popularity of the capsule should not be surprising. For instance, because the medication is contained within the capsule shell, the capsule provides a tasteless, odorless delivery system that doesn't require a secondary coating step. Many patients find that swallowing capsules is easier than swallowing tablets. Furthermore, several surveys have revealed a generally favorable consumer attitude toward

Input package

The components of an input package are

- name of the drug
- particle size (μm)
- solubility (mg/mL)
- specific surface area (m^2/g)
- intrinsic dissolution rate ($mg/min/cm^2$)
- desired tolerance and confidence limits for content uniformity
  - tolerance = (±z) (% CV)
- dose (mg) and permeability (cm/s)
- tapped density (g/mL).

Simplified filler system

The components of a simplified filler system are

Drug dose volume: >250 mL <1000 mL

Filler F-Sol: fine particle size
- 50% anhydrous lactose (fine grade)
- 50% Emcocel 50

Filler M-Sol: medium particle size
- 50% anhydrous lactose (medium grade)
- 50% Emcocel 90M

Drug dose volume: >1000 mL

Filler F-Insol: fine particle size
- 75% anhydrous lactose (fine grade)
- 25% Emcocel 50

Filler M-Insol: medium particle size
- 75% anhydrous lactose (medium grade)
- 25% Emcocel 90M.

capsules (1,2). From the formulator's point of view, hard-shell capsules provide unique capa-bilities and options for dosage form design and formulation. For instance, there is no need to design a compact that must withstand the handling needed for a compressed tablet. Thus, with the appropriate choice of excipients, it may be possible to direct-fill into capsules many large-dose actives that could not be tableted without a granulation step. Modern capsule-filling machines also enable the multiple filling of beads, granules, tablets, powders, and pumpable liquids into hard shells. This capability provides the formulator with numerous options for designing unique delivery systems or simply for separating incompatible substances within the same capsule.

Even though hard gelatin capsules are perceived to be a simple dosage form, the design of formulations for the capsules can present significant challenges to the formulator. For example, problems such as ingredient compatibility and stability, powder blending and homogeneity, and powder fluidity and lubrication are frequently encountered and must be addressed during any attempt to design production-feasible formulations. The ability to measure accurate and precise volumes of a powder or granular mass and the ability to quantitatively transfer such dry solids to capsule shells are the determining factors in weight variation, and to a degree, content uniformity. In addition, the same formulation may be required to run on machines that use different dosing principles and have various operating characteristics. Not only must formulations be designed to successfully run in the production environment, but their ability to function as drug delivery systems must not be compromised by poor formulation design and failure to properly account for the interplay of formulation and process variables.

Instrumented capsule-filling machines (3–6) enable the measurement of force-displacement relationships in plug formation and ejection and have supported the development of capsule-filling-machine simulation (7,8). These developments have provided important insights into the interplay between formulation and machine-operating variables that, when coupled with an understanding of biopharmaceutical principles (9) and powerful software-driven decision-making and optimization tools, lead to logical and deliberate decisions to facilitate systematic formulation design. This article addresses the application of decision-making tools such as expert systems (ESs) and artificial neural networks (ANNs) to the development of optimal formulations for hard gelatin capsules.

Artificial intelligence systems in the form of ESs have begun to be used only to provide support for the formulation process. An ES is an intelligent computer program that attempts to capture the expertise of those who have knowledge and experience in a well-defined domain (e.g., capsule formulation) (10). It is designed to simulate the experts' problem-solving process. A well-designed ES can shorten development time, simplify formulations, provide the rationale for decisions made while arriving at a formulation, serve as an excellent teaching tool for novices, and accumulate and preserve the knowledge and experience of experts. However, ESs are not creative—they can deal only with situations that have been anticipated. They must be designed to handle every contingency.

Another form of artificial intelligence is the ANN. ANNs are computer programs that attempt to simulate certain aspects of human thinking such as learning, generalizing, predicting, or abstracting from experience (11). They can discern relationships of patterns in response to exposure to facts (i.e., learning). With ANNs, the data and information generated during experimental work may be transformed relatively easily into knowledge, enabling the formulator to at least construct a few domain-specific rules for future cases or to predict the properties of a hypothetical formulation.

CAPEX, Capsugel's ES for formulation support, is a centralized system that incorporates worldwide industrial experience to support the formulation of powders in hard gelatin capsules (12,13). With Capsugel's sponsorship, this program was started at the University of London and later was supported by efforts of the University of Kyoto and the University of Maryland. From its origins at the University of London, this ES has been under continuous development and enhancement through additional research and a series of panel meetings in Europe, Japan, and the United States that involve industrial, regulatory, and academic experts. In addition, the system's conversion to a Microsoft Windows–based platform significantly enhanced its ease of use by formulators. However, it cannot be said that the evolutionary development of the system is complete. Expert panel meetings continue to identify areas that must be enhanced.

Ostensibly, a formulation recommended by CAPEX will run successfully, but one cannot be certain unless it is tried. In fact, "to run successfully" is never defined. For example, one might ask whether the recommended formulation can run in any machine or whether the recommended formulation meets content uniformity and weight variation specifications. Not only must formulations be designed to successfully run in the production environment, but they also must be able to meet their design criteria in other areas, particularly in how they function as drug delivery systems. The current CAPEX system provides no guidance or assurance that the recommended formulation will meet a particular drug release (i.e., dissolution) requirement as well as exhibit content uniformity or weight variation within user-specified limits.

A proposal has been made to use an intelligent hybrid system to link the current ES to an ANN (see Figure 1). Potentially, this system can address the above two limitations and provide

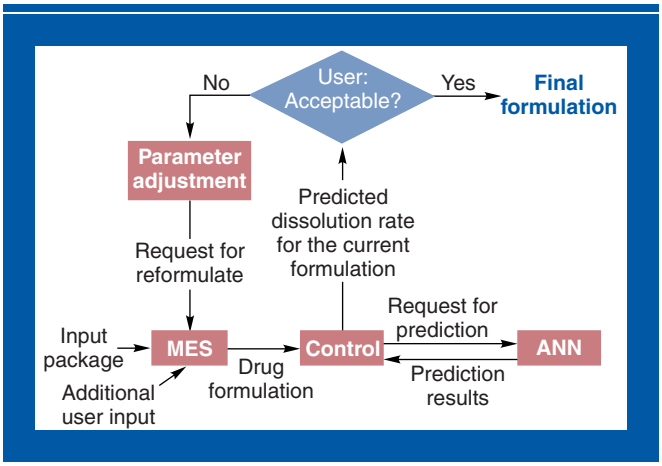

Figure 1: An overview of a hybrid system.

Table I: Parameter adjuster. The following parameters may be changed by the user during reformulation.

Formulation Parameter	Range	Minimum Amount Allowed to Change
MCC*/anhydrous lactose	10–100	5%
SSF**/MS†	0–100	10%
Particle size	5–150	10%
Lubricant level	0.2–2.0	0.1%
Wetting agent	0.1–1.0	0.1%
Disintegrant	4.0–12.0	2.0%

*MCC = microcrystalline cellulose
**SSF = sodium stearyl fumarate
†MS = magnesium stearate.

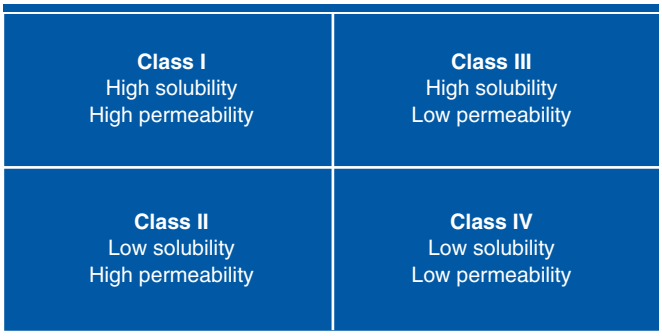

Figure 2: Biopharmaceutics Classification System.

a facilitated way to generate new rules on the basis of "learning." Moreover, the development of a hybrid system that integrates an ANN with an ES can take advantage of the strengths of both systems and avoid the weaknesses of either (10,14).

Early on, the panel of experts decided to focus on Class II drugs as described in the Biopharmaceutics Classification System (BCS) (see Figure 2). The BCS organizes orally administered drugs into four classes according to their solubility (high or low) and permeability (high or low), thereby giving formulation scientists the ability to judge the likely contribution of dissolution rate, solubility, and intestinal permeability to oral drug absorption (9). Solubility is expressed in both BCS and MES as a dose volume (i.e., the minimum volume in mL of solvent required to dissolve the dose). In the BCS, a drug is considered to have low solubility if the dose volume calculated from its minimum solubility in the pH range of 1–8 at 37° is greater than 250 mL for the largest strength manufactured. If that value is ⩽250 mL, the drug is considered to have high solubility. Class I drugs (high solubility and high permeability) are likely to exhibit few bioavailability problems, but Class II drugs (low solubility and high permeability) are prone to dissolution rate–limited absorption. Class III drugs (high solubility and low permeability) are likely to exhibit permeation rate–limited absorption. Class IV drugs (low solubility and low permeability) may present serious obstacles to oral bioavailability, and some may be best formulated in a solubilized form such as a liquid-filled or semisolid-filled capsule. For Class II drugs, however, the dissolution rate clearly is a critical parameter that must be monitored because it may directly affect oral bioavailability. Thus, during the development of the prototype hybrid system, piroxicam (low solubility and high permeability) was chosen as the model drug to represent BCS Class II, and the dissolution rate was chosen as the dependent factor to monitor any effects of changes in the formulation parameters.

To scale down the magnitude of this effort, the panel proposed first to develop a model expert system (MES) modeled on the CAPEX system (see Figure 3). The MES was to be similar to the CAPEX system but limited in scope. The panel expected that given certain input information (see "Input package" sidebar), the MES could make choices within a limited space and recommend a formulation. Its known source code would enable and facilitate the development of an appropriate link to the ANN.

Because the objective of this research was to demonstrate the feasibility of developing a hybrid system through the creation of a working prototype, the following simplifying assumptions were made in the development of the MES:

- Only directly fillable formulations were considered (i.e., granulation was not an option).
- No incompatibilities existed between the excipients and the active ingredient.
- A simplified blend-uniformity model could be applied.
- Fillers could be simplified to microcrystalline cellulose (MCC)–anhydrous lactose blends. If low dose, more anhydrous lactose is required; if high dose, more MCC is required to enhance the compactability of the formulation (e.g., if drug has lower solubility, more anhydrous lactose is expected to aid dissolution. If drug particle size is smaller, a finer particle-size grade of filler is selected to help maintain blend uniformity. If the dose is high, more MCC may be required to enhance the compactibility of the formulation) (see "Simplified filler system" sidebar and Figure 2).

Materials and methods

Materials and encapsulation conditions. Piroxicam was supplied by Pfizer (Groton, CT), and MCC (Emcocel 90M and Emcocel 50) was obtained from Penwest Pharmaceuticals Co. (Patterson, NY). Anhydrous lactose (direct-tableting grade) was purchased from Quest International (Norwich, NY). Fine-

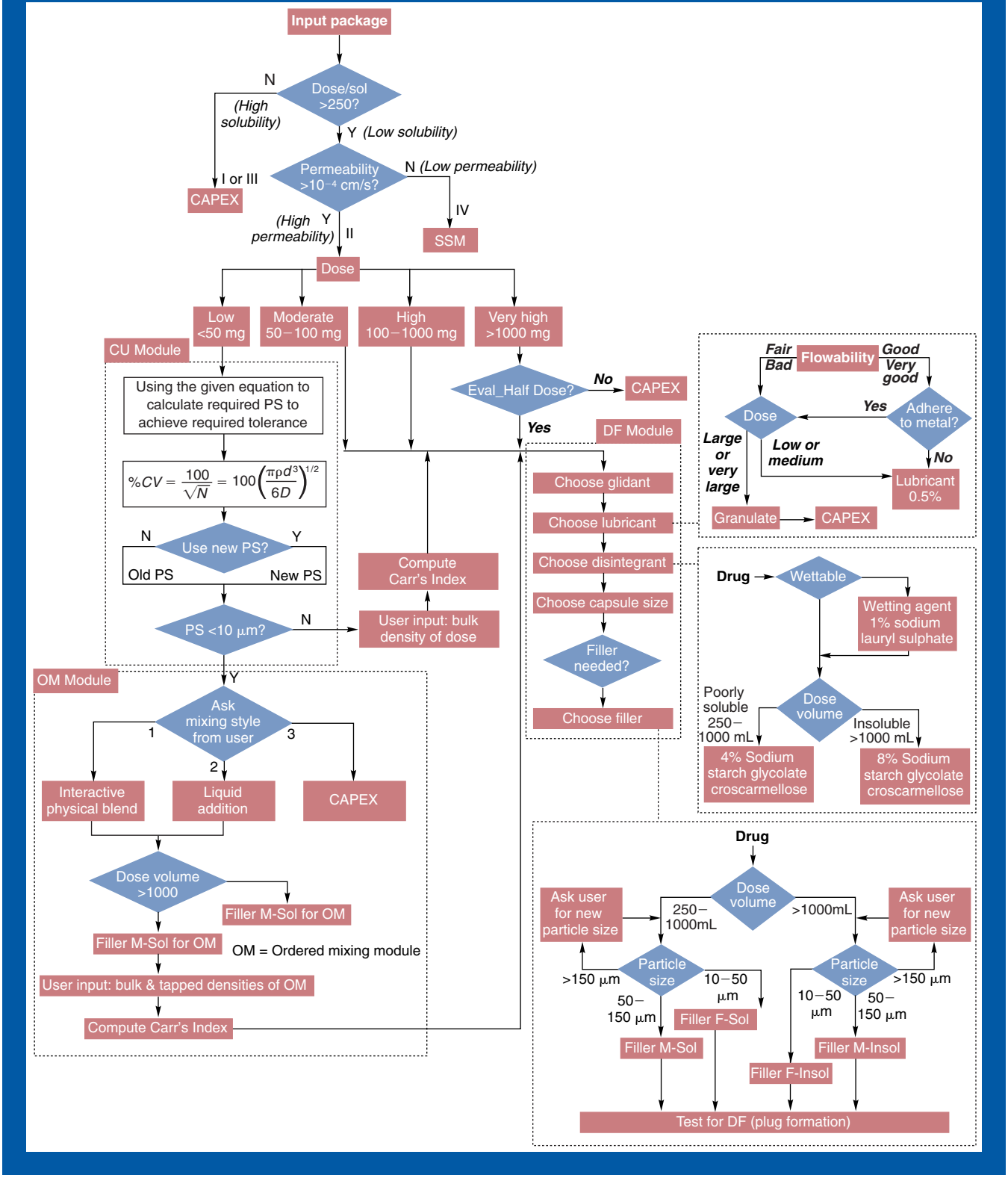

Figure 3: The algorithm of a model expert system (MES).

particle-size anhydrous lactose was prepared by passing the latter product through a 100-mesh sieve.

A fully instrumented Zanasi LZ/64 dosator machine (IMA North America, Fairfield, CT) was used to manufacture the capsules (4,15). Data were acquired by means of a laboratory computer using LabView hardware and software (National Instruments, Inc., Austin, TX). During encapsulation, the compression force was maintained at ~120 N. All capsules were size 1 (Capsugel, Greenville, SC). The typical batch size was 1 kg. All batches were prepared according to uniform procedures. All excipients and piroxicam were of USP–NF grade. The dose of piroxicam was 20 mg/capsule. After the encapsulation process was stabilized as indicated by monitoring the compression/ejection–time profile on the instrumentation system, 50 capsules were col-

lected. The sample capsules were stored in a plastic bag for future use.

Dissolution testing. Dissolution was performed on a VanKel VK7000 apparatus (VanKel, Edison, NJ). A peristaltic pump (Rainin Instrument Co. Inc., Woburn, MA) was coupled to a Shimadzu UV-160U UV–vis spectrophotometer (Shimadzu Corp., Kyoto, Japan) with continuous flow to provide drug dissolution data. Dissolution conditions were as prescribed for piroxicam in *USP–NF* (16): Apparatus I at 50 rpm and a dissolution medium of simulated gastric fluid TS without pepsin. The percentages of piroxicam dissolved in 10, 30, and 45 min were reported as the means of six determinations.

Measurements of specific surface area. Specific surface areas of piroxicam were measured by using FlowSorb II 2300 (Micromeritics, Norcross, GA), and the reported values are the means of three measurements.

Measurement of plug-breaking force. Plug-breaking forces were measured using the 3-point flexure tester previously constructed at the University of Maryland and described by Shah et al. (17). Ten readings were averaged for each run.

Measurement of Carr's compressibility index (CI). As will be discussed, the flowability of formulations was estimated on the basis of CI (18). The CI was calculated from the tapped (ρ_t) and loose (ρ_b) bulk densities as follows:

$$CI = \frac{(\rho_t - \rho_b)}{\rho_t} \times 100$$

The tapped and loose bulk densities were estimated by the method described in *USP–NF* (16) using a Scott, Schaeffer, and White paint pigment volumeter (Fisher Scientific, Springfield, NJ) and the Stampf volumeter (Shandon Southern Instruments, Inc., Sewickley, PA), respectively.

Table II: Central composite design.

Pattern	Block	X_1	X_2	X_3	X_4	X_5	Comment
−−−−+	1	−1	−1	−1	−1	1	FF
−−−+−	1	−1	−1	−1	1	−1	FF
−−+−−	1	−1	−1	1	−1	−1	FF
−−+++	1	−1	−1	1	1	1	FF
−+−−−	1	−1	1	−1	−1	−1	FF
−+−++	1	−1	1	−1	1	1	FF
−++−+	1	−1	1	1	−1	1	FF
−+++−	1	−1	1	1	1	−1	FF
+−−−−	1	1	−1	−1	−1	−1	FF
+−−++	1	1	−1	−1	1	1	FF
+−+−+	1	1	−1	1	−1	1	FF
+−++−	1	1	−1	1	1	−1	FF
++−−+	1	1	1	−1	−1	1	FF
++−+−	1	1	1	−1	1	−1	FF
+++−−	1	1	1	1	−1	−1	FF
+++++	1	1	1	1	1	1	FF
0	1	−2	0	0	0	0	Axial
0	1	2	0	0	0	0	Axial
0−000	1	0	−2	0	0	0	Axial
0+000	1	0	2	0	0	0	Axial
00−00	1	0	0	−2	0	0	Axial
00+00	1	0	0	2	0	0	Axial
000−0	1	0	0	0	−2	0	Axial
000+0	1	0	0	0	2	0	Axial
0000−	1	0	0	0	0	−2	Axial
0000+	1	0	0	0	0	2	Axial
0	1	0	0	0	0	0	Center-Ax
0	1	0	0	0	0	0	Center-Ax
0	1	0	0	0	0	0	Center-Ax
0	1	0	0	0	0	0	Center-Ax
0	1	0	0	0	0	0	Center-Ax
0	1	0	0	0	0	0	Center-Ax

System design and architecture

A rule-based ES was developed in the Prolog computer language and integrated with an ANN. These two components, which comprise the decision module and the prediction module, respectively, are connected by two information-exchange paths to form a loop. The hybrid ES has three major components: the MES module, the ANN module, and the control module. The function of the MES is to make a recommended formulation on the basis of the input package provided by users. The following sections in this article will discuss each major component of the MES. The control module sends the recommended formulation to the ANN module, and the ANN predicts the dissolution performance of the recommended formulation. Once the control module receives the prediction from the ANN, it compares the prediction with the desired target dissolution performance and decides whether it is acceptable. If the predicted dissolution performance does not meet the desired target, then the control module provides guidance to improve dissolution and sends the information to the MES to require reformulation. The control module guides the optimization process until either a satisfactory formulation is found or the optimization is terminated by the user.

In addition to the three major components, another necessary module is the parameter-adjustment module, which adjusts the formulation parameters when the control module rejects the recommended formulation (see Figure 1 and Table I). For immediate-release capsule formulation, the most common problem is to increase the dissolution rate; thus, the parameters will be changed in the specified manner to cause the dissolution rate to increase. Moreover, only one parameter, chosen by the user, is allowed to change at a time, and each time the chosen parameter changes by a fixed amount or percentage that is predetermined according to each parameter.

MES. MES, the formulation decision module, provides decision rules for formulation recommendation. After reading input from users, the MES derives a recommended capsule formula-

Table III: Chakravarty design.

	X_1	X_2	X_3	X_4	X_5	X_6	X_7
1	−1	−1	−1	−1	−1	−1	−1
2	−1	−1	0	0	1	0	0
3	−1	−1	1	1	0	1	1
4	−1	1	−1	0	0	0	1
5	−1	1	0	1	−1	1	−1
6	−1	1	1	−1	1	−1	0
7	−1	1	−1	1	1	0	−1
8	−1	1	0	−1	0	1	0
9	−1	1	1	0	−1	−1	1
10	1	−1	−1	1	0	−1	0
11	1	−1	0	−1	−1	0	1
12	1	−1	1	0	1	1	−1
13	1	1	−1	−1	1	1	1
14	1	1	0	0	0	−1	−1
15	1	1	1	1	−1	0	0
16	1	1	−1	0	−1	1	0
17	1	1	0	1	1	−1	1
18	1	1	1	−1	0	0	−1

Table IV: Box-Behnken design.

Pattern	Block	X_1	X_2	X_3
0	1	−1	−1	0
0	1	−1	1	0
0	1	1	−1	0
0	1	1	1	0
0−−	1	0	−1	−1
0−+	1	0	−1	1
0+−	1	0	1	−1
0++	1	0	1	1
−0−	1	−1	0	−1
+0−	1	1	0	−1
−0+	1	−1	0	1
+0+	1	1	0	1
0	1	0	0	0
0	1	0	0	0
0	1	0	0	0

tion on the basis of the input package provided by the user. In addition, it conducts the reformulation task when the control module rejects the initial recommended formulation. At first, when an MES receives the input package, it generates a random number to be the unique identification (ID) to reference for this drug during inference. The MES also converts the drug specifications in the input package to Prolog predictions (with the ID tag) and inserts them into the knowledge base as facts. After this preparation, the drug's BCS classification is determined. If it is a Class II drug, then the MES is used; otherwise one implements the CAPEX system.

Inside the MES formulation system, the process of deriving the recommended formulation uses various modules on the basis of information from the input package and the user's responses to questions. To improve the efficiency of the hybrid system, the MES has been programmed into various routes according to the dose range, i.e., low, moderate, and high dose. For low-dose drugs (<50 mg), the MES proceeds first through the content-uniformity module to determine whether it is necessary to change the particle size of the active ingredient to meet the required limit of content uniformity (19,20). Also for the low-dose formulation, the ordered mixing module will ensure that an appropriate procedure is chosen to achieve the requisite blend uniformity (21,22). Three blending methods are suggested: interactive physical blending, liquid addition, and wet granulation. The user selects one method and, after executing that process, must enter the potency and the tapped and bulk densities of the resulting ordered mix before the MES can continue on to the direct-fill (DF) module. Because ordered mixing generally is not required for moderate- (50–100 mg) and high-dose (100–1000 mg) drugs, such drugs go directly to the DF module to be formulated. For very high dose drugs (>1000 mg), the MES suggests cutting the dose in half before moving into the DF module. If the latter is not acceptable to the user, then granulation will be required and the MES sends the user out of the system. As discussed previously, granulation has not been included in this prototype.

In the DF module all formulation parameters are to be defined such as the levels of glidant, lubricant, disintegrant, diluent, the capsule size, and the filler. Moreover, the DF module provides a feedback loop on the basis of attaining at least a specified minimum plug mechanical strength. If the user cannot attain that value, then the MES sends the user out of the system to consider granulation. As shown in Figure 3, all formulation parameters are defined according to the drug's flowability, wettability, and dose volume in relation to solubility and particle size. After completing these computing and reasoning steps, the MES provides the capsule size and respective weight of each component of the recommended formulation.

Unlike other ESs that are constructed with decision trees, this MES is constructed as a rule-based system, encoded in Prolog. Such implementation gives an MES quite a few advantages over other ESs. First, knowledge is separated from the inference engine, thus the designer must provide only the knowledge base because the inference mechanism is provided by the language package. Second, the modularity of knowledge coding is an advantage. The rules are local and relatively independent of the inference engine, thus making it easy to maintain and update the knowledge base. Third, a Prolog rule-based system is more expressive than a decision-tree system, i.e., it can represent more-complicated decision logic and more-abstract situations, thereby providing the system with broader applicability to complex formulation problems. Finally, the Prolog rule-based system has strong programming support. Because Prolog is the primary language for knowledge-based system development, it is easy to find tools to interface with code in other computing languages (e.g., VB, C, Java), which leaves more room for flexible interface design and further development.

ANN. The ANN module, using backpropagation learning (11), is the property prediction module that maps the relationship between formulation parameters and the desired response. In this case, dissolution has been mapped. On the basis of that mapping, the ANN provides a prediction of the dissolution performance of the formulation recommended by the MES. The

Summary of the variables and levels of the training data set

Experimental batches: 66
Responses (output fields): 3
Percent dissolved in 10, 30, and 45 min
Independent variables (input fields): 9

- Filler particle size (μm) (60, 100)
- Disintegrant type (Explotab, Ac-Di-Sol)
- Lubricant level, percentage (0, 0.3, 0.5, 0.6, 0.7, 1.0)
- Lubricant (binary mixture of SSF and MS) (% SSF) (0, 50, 100)
- Percentage of anhydrous lactose in anhydrous lactose–MCC blend (0, 50, 100)
- Percentage of disintegrant level (3, 4, 5, 6, 8, 9, 12)
- Wetting agent, percentage of sodium lauryl sulfate (0, 0.2, 0.3, 0.5, 0.6, 0.7, 1.0)
- Specific surface area (piroxicam) (m^2/g) (1.61, 2.46, 2.77, 3.31)
- Lubricant blending time (min) (2, 3, 10, 18).

only way the ANN can map out the causal association between the formulation and the outcome in the capsule formulation system is through a training process using experimental data. For the ANN to have sufficient predictive power, it is extremely important that sufficient data from well-designed experiments are provided to train the ANN. In the present research, that training was conducted with three experimental data sets using piroxicam as the model drug. The data sets represent response surface designs developed to reflect the mapping from variables such as filler type–ratio, lubrication systems, drug particle size–specific surface area, disintegrants and surfactants, to the dissolution of the model compound.

The neural network architecture used in the ANN module is a backpropagation learning network. This network learns accurate mapping between input and output patterns in the training samples by error backpropagation and computes the output from a given input pattern by forward computing. The training of a network by backpropagation involves three stages: the feedforward of the input training pattern, the calculation and backpropagation of the associated error, and the adjustment of the weights. After training, application of the ANN involves only the computations of the feedforward phase.

Control module. Driven by the discrepancy between the desired and predicted outcomes, the control module controls the entire optimization process in the hybrid ES. The control module converts the formulation from the MES to input to the ANN and then calls the ANN module to compute the predicted dissolution rate. It also asks for the user's acceptance of the currently recommended formulation on the basis of the predicted dissolution rate. If the user authorizes acceptance of the formulation, then the control module will terminate the formulation process and send the recommended formulation out, although this is not the usual case. In most instances, the control module compares the predicted performance of the recommended formulation with the desirable properties of the target formulation and decides whether the recommended formulation is acceptable, and if not, what should be done to improve it. Then it will present a set of choices of parameter adjustments to users for improving the dissolution rate and later reenters the MES for reformulation with the parameter adjustment(s) selected by the user. The control module then repeats this procedure until either a satisfactory formulation is found that meets the desired dissolution requirement or the optimization is terminated by the user.

Training data set and training

As mentioned previously, the quality of the training data and the number of batches will affect the prediction power of the ANN dramatically. Considering the high cost of experimental batches, the best way to deliver as much information as possible in a given series of experimental batches is to use statistical experimental design to develop and generate the training data. In the present study, three experimental designs were applied: central composite (face centered) as described in Table II, L18c-Chakravarty as described in Table III, and Box-Behnken as described in Table IV. The first set of batches was previously reported data generated from the same laboratory and used the same procedures and the same capsule-filling machine (23). The surface area of the piroxicam samples was measured to normalize all training batches, and it also was used in the training data set as an independent variable.

Nine independent variables were investigated, and the dissolution rate, expressed as percentage of piroxicam dissolved in 10, 30, and 45 min, was monitored as the dependent variable. The capsules were filled using a dosator-type automatic filling machine. A total of 63 experimental batches was used to train the ANN. The sidebar "Summary of the variables and levels of the training-data set" lists the independent variables and their levels.

The training parameters (number of hidden layer, hidden nodes, type of training function, training time, training rate, and training slope) can greatly affect the prediction power of the trained ANN. By exploring various combinations of these parameters while monitoring the system error, the optimum values for these training parameters were chosen on the basis of maintaining the lowest system error. The values are

- input layer: 9 neurons
- output layer: 3 neurons
- hidden layer: 9 neurons
- activation function: sigmoid
- training time: 2 K
- training slope: 0.2
- training method: sequential training.

Validation of the hybrid system

The best available method to check the predictability of an ANN and test the functionality of the hybrid system is cross-validation. Typically, 8–10% of all available samples are randomly selected and set aside to serve as the cross-validation set. The cross-validation set thus does not participate in training; instead, these data serve as test samples with which to challenge the predictability of the trained ANN. In the present study, data from five batches (~8% of the total number of available batches) were set aside for cross-validation. The data from the remaining 58 batches were used to train the ANN in optimal training conditions. The trained ANN then was used to predict the dissolution performance of the five batches that

Table V: Model statistics of the training in the validation.

Validation result					
Validation sample	8 independent parameters, 8% test samples				
Training condition	hidden layer	1			
	hidden nodes	9			
	slope	0.2			
	max system error	0.00002			
	max iteration	2000			
Model statistics					
Train set D10	**Source of Variation**	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed *f* Ratio**
	Model	5180.478419	91	56.928334	−20.054639
	Error	82.321186	−29	−2.838662	
	Total	5263.05686	62		
Train set R^2 = 98.435867					
Train set D30	**Source of Variation**	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed *f* Ratio**
	Model	4890.023722	91	53.736524	−113.335896
	Error	13.749917	−29	−0.474135	
	Total	4892.435171	62		
Train set R^2 = 99.718956					
Train set D45	**Source of Variation**	**Sum of Squares**	**Degrees of Freedom**	**Mean Squares**	**Computed *f* Ratio**
	Model	4378.119973	91	48.111208	−25.734494
	Error	54.216145	−29	−1.869522	
	Total	4673.725971	62		
Train set R^2 = 98.83998					

D10 = Percentage of piroxicam dissolved in 10 min.
D30 = Percentage of piroxicam dissolved in 30 min.
D45 = Percentage of piroxicam dissolved in 45 min.

Table VI: The validation result.

D10	D10 (predicted)	Error	D30	D30 (predicted)	Error	D45	D45 (predicted)	Error
64.98	65.35	−0.37	82.66	80.69	1.97	85.50	85.72	−0.22
63.76	57.93	5.83	77.02	70.96	6.06	79.49	75.71	3.78
67.07	61.64	5.43	80.65	75.70	4.95	85.19	80.47	4.72
59.06	63.45	−4.39	86.88	87.54	−0.74	92.62	92.96	−0.34
72.05	65.38	6.67	90.84	89.92	0.92	95.31	94.74	0.57

D10 = Percentage of piroxicam dissolved in 10 min.
D30 = Percentage of piroxicam dissolved in 30 min.
D45 = Percentage of piroxicam dissolved in 45 min.

Table VII: Validation of a hybrid system.

D10	Experiment	Error	D30	Experiment	Error	D45	Experiment	Error
67.55	71.01	3.46	86.54	94.43	7.89	97.11	99.07	1.96
67.88	66.55	1.33	87.00	92.23	5.23	96.60	96.69	0.09
72.27	72.41	0.14	90.64	94.94	4.30	95.99	98.73	2.74

D10 = Percentage of piroxicam dissolved in 10 min.
D30 = Percentage of piroxicam dissolved in 30 min.
D45 = Percentage of piroxicam dissolved in 45 min.

were set aside and not used in the training of the ANN. The predicted performance then was compared with the experimentally determined dissolution data for these batches.

First the model statistics were checked during the training. Model statistics data as listed in Table V show that the training parameters chosen led to very low system error. In other words, the value of the training set R^2 is very close to 100. The comparison data as listed in Table VI reveal that the percent dissolved at 10 min for four of the five validation sets all were within 5.8%. For all validation batches, the percent dissolved at 30 min was within 6.8%, and the percent dissolved at 45 min was within 4.7%. Considering the normal variability of real dissolution data, an ANN may be reasonably capable of both mapping out the relationship among the formulation parameters

and dissolution rate and making an acceptable prediction of dissolution performance for the drug in question.

As stated earlier in this article, the ultimate goal of the hybrid system is to help product-development scientists design a formulation to meet certain design criteria. The development of an ANN with suitable predictability achieves only part of that goal. The hybrid system should be able to design a formulation on the basis of the design criteria, and experimental testing of the recommended formulation should match the design criteria and confirm the prediction of the ANN. To validate this capability, the hybrid system was tested by manufacturing and laboratory testing of the predicted formulations. Three target dissolution rates were fed into the system, and three batches of capsules were made on the basis of the formulations recommended by the hybrid system. These formulations were manufactured and tested using the previously described methods and procedures. The experimental results were compared with the design criteria; Table VII lists the data. This comparison reveals that for the percentage of drug dissolved in 10 min, the differences between the design criteria and the experimental result are $<3.46\%$; for the percentage dissolved at 30 min, the differences are $<7.89\%$; and for the percentage dissolved at 45 min, the differences are $<2.74\%$. These results demonstrate that the hybrid system can map out the relationship between the formulation variables and piroxicam dissolution from direct-filled hard gelatin capsules. It also can predict the dissolution rate of the capsule formulation with good accuracy and derive the recommended formulation to match the design criteria.

Conclusion

A prototype intelligent hybrid system was created for developing direct-fill formulations for hard gelatin capsules by linking a decision module (i.e., an ES) with a prediction module (i.e., an ANN). Through validation, the hybrid system was proved capable of yielding formulations of a model BCS Class II drug, piroxicam, that meet specific drug dissolution performance criteria. Although this research was limited to a single drug, it is believed that the system can be generalized to be predictive of other BCS Class II drugs, perhaps on the basis of the wettability, intrinsic dissolution rate, and other properties of drugs within certain subclasses. Research aimed at generalization to other BCS II drugs is currently ongoing in our laboratory.

Clearly, the integration of a decision module with a prediction module potentially can support functions beyond the current ES (CAPEX) that would significantly enhance formulation development. The most important among these is the implementation of a formulate-and-evaluate cycle that simulates the product-development process of the human formulator. Thus, formulation development no longer would be a one-step process as it is with CAPEX, but rather an iterative process in which a formulation can be incrementally improved. The quality of the output can be improved further by taking advantage of the learning capability of the system, which would allow the decision process to be modified on the basis of its past performance. The framework of such a hybrid system also could be extended to incorporate other intelligent modules such as optimization or the development of other dosage forms.

Acknowledgments

The authors gratefully acknowledge Capsugel, a Division of Pfizer Inc., for financial support and Pfizer Central Research for the gift of piroxicam.

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