Development of Generic Drug Tablet Production Expert System

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Abstract

In this paper, we develop an expert system for generic name drug in tablet dosage form. The expert system recommends a tablet production that consists of a list of ingredients, their quantity, and a set of manufacturing instructions. Domain knowledge which contains information of excipients and tablet productions in modelbases was built based on tablet production ontology. Domain knowledge is incorporated with operation knowledge in production rules to recommend a generic drug production that is pharmaceutical equivalent to the original drug.

1 Introduction

The development of new drug entities in Thailand is difficult because of the lack of funds, technology and persons. Thai pharmaceutical industry therefore focuses on generic drug formulations according to increasing demand of the world market.

Pharmacists in the manufactuers of generic drug product have to formulate generic drugs that contain the same active ingredient, quality, therapeutic efficacy, safety and performance as its brand name counterpart. They must show that their formulations are pharmaceutical equivalent and/or bioequivalent to the original drug (Shargel L. and Kanfer I., 2005). The pharmaceutical equivalence is comparing dissolution profiles between the original drug and a generic drug. The generic drug is pharmaceutical equivalent to the original drug when difference factor (f_1) and similarity factor (f_2) are in ranges.

The generic drug formulation is a highly specialized task requiring specific knowledge and years of experience (Rowe RC and Roberts RJ., 1998). Expert system is recognized as a system that assists the pharmacists to formulate generic drug and raise productivity, consistency and quality. There are many expert systems for a development of pharmaceutical formulations. They have been designed to formulate pharmaceutical products for new drug entities based on their physical (e.g. solubility, hygroscopicity), chemical (e.g. functional groups) and biologically inter-related (e.g. dissolution rate) properties. The expert systems of pharmaceutical formulation have two types of knowledge structure: (1) decision tree and production rules, and (2) object, frame and production rules. Knowledge structure cannot be shared and reused among other systems althought it have the same dosage form domain (e.g., tablet, capsule, injection). All of the expert system represents pharmaceutical formulations as only a list of ingredient and its quantity. They do not represent a set of instructions that explain how to manufacture pharmaceutical product.

The objective of this paper is to develop an ontology based expert system which is able to recommend a production of a generic drug tablet to industrial pharmacists. The system provides a list of ingredients, quantity and a set of instruction which pharmaceutically equals to the original drug.

2 Background

The first recorded reference to the use of expert systems in pharmaceutical product formulation was by Bradshaw, closely followed by Walko. Several companies and academic institutions have reported on their experiences in development of pharmaceutical formulation expert systems as shown in Table 1 (Rowe RC and Roberts RJ., 1998).

All of the expert system of pharmaceutical product formulation has been designed based on physical, chemical, biologically inter-related properties of active ingredient and predicted properties of pharmaceutical product. The main

Table 1. Published application of pharmaceutical product formulation expert system

COMPANY/INSTITUTION	DOMAIN	DEVELOPMENT TOOL
Cadila Laboratories(India)	Tablets	PROLOG
University of Lodon/Capsugel	Capsules	C
University of Heidelberg	Aerosols Tablets Capsules IV injection	C/SMALLTALK
Zeneca Pharmaceuticals	Tablets Parenterals Film coatings	Product Formulation Expert System(PFES)
Sanofi Research	Capsules	PFES
Boot Company	Topicals	PFES

output of these systems is formulation that consists of a list of ingredients and its proportion as shown in Table 2. However, the different points of these systems are dosage form domain, development tool and knowledge representation. The knowledge representation of Galenical development system, Sanofi system, Zeneca system, and Boots system is in objects, frames and production rules, on the other hand, the knowledge representation of Cadila laboratories's system and Capsugel system is in decision table and rules.

Table 2. Example of tablet formulation for a model drug as generated by the Zeneca System

DRUG A	50.0 MG	150 MG.
Lactose monohydrate	166.9 mg.	-
Dicalcium phosphate dehydrate	-	165.7 mg.
Croscarmellose sodium	4.8 mg.	7.0 mg.
Polyvinyl pyrrolidone	4.8 mg.	-
Hydroxypropyl methylcellulose	-	7.0 mg.
Sodium lauryl sulphate	0.7 mg.	1.1 mg.
Magnesium stearate	2.4 mg.	3.5 mg.
Tablet diameter	8.0 mm	10.0 mm

3 System Framework

The framework of an expert system is shown in Figure 1. The framework is made up of four modules which are knowledge base, inference engine, user interface, and developer interface. The knowledge base module consists of domain knowledge of tablet recipes and operational knowledge of rules. The domain knowledge was constructed based on tablet production ontology. The information of original drug tablet from user is initially collected. Next, the expert system retrieves the generic name drug tablet formulation that is closed to the target formulation from

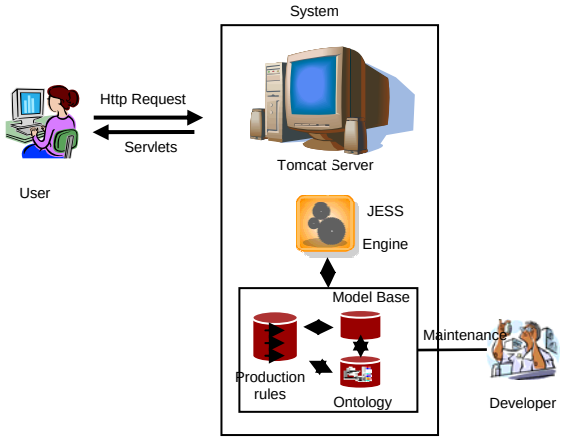

Figure 1. The Generic Drug Tablet Production Expert System Framework

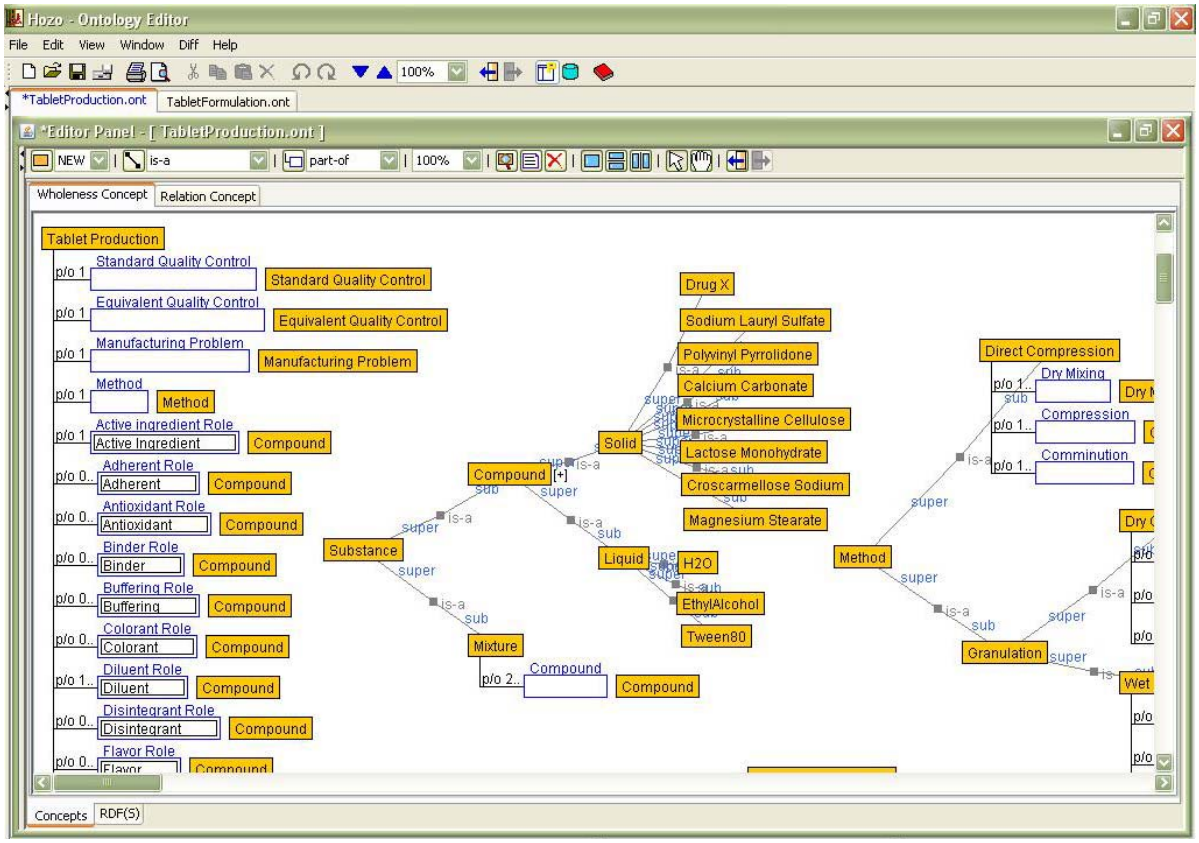

Figure 2. The Tablet Production Ontology

database (domain knowledge). Then, it applies rules represented in JESS engine (Ernest Friedman-Hill, 1990) to recommend the most appropriate tablet formulation that is pharmaceutical equivalent to the original tablet formulation.

4 Knowledge Acquisition and Knowledge Representation

Knowledge representation of the expert system can be divided into two groups, domain knowledge and operation knowledge. Domain knowledge contains information of excipients following the Handbook of Pharmaceutical Excipients (Raymond C. Rowe et al., 2005) and modelbases of tablet productions. Modelbase of tablet production was generated from literature and patent reviewing information (e.g. drug and excipient lists, incompatibility and stability of drug) based on the tablet production ontology (Nopphadol Chalortham et al, 2008). The tablet production ontology is shown in Figure 2. We use the Hozo environment to develop ontology in the expert system (Kouji Kozaki et al., 2002). It is composed of ontology editor and model editor. The tablet production ontology consists of a list of ingredients and their quantity, and a set of instructions that explain how to manufacture tablet in laboratory scale. Modelbase of tablet productions in XML pattern is transformed to Lisp language and loaded in JESS engine memory. The modelbases of tablet production integrate with operation knowledge for recommending generic drug tablet productions.

The operation knowledge in production rules was collected from experience of experts and generic drug tablet formulation experiments. The operation knowledge is designed to formulate the generic name drug tablet based on; (1) active drug's preformulation study such as physiochemical properties and (2) the original drug formulation properties such as disintegration time, dissolution profile.

The components of production rules are represented in the form:

IF <*condition*> THEN <*action*>.

When the <*condition*> is triggered the <*action*> will be executed. An example of a simple production rule in the generic drug tablet production expert system would be like:

IF (*disintegration time of the generic drug formulation is more than disintegration time of the original drug formulation*)

And (*friability of the generic drug formulation is between 0.5 and 1%*)

THEN (*increase concentration of disintegrant*).

5 Generic Drug Tablet Production Expert System

Pharmacists in the generic drug manufacture input the information of trade name drug and/or a generic name drug production. The system evaluates the generic name drug production comparing with the trade name drug formulation. If the generic name drug production pharmaceutically equals the trade name drug formulation, user will examine stability of the generic name drug formulation and/or scale up to larger batch in the next phase of pharmaceutical product development. Conversely, if the generic drug production does not pharmaceutically equal the trade name drug formulation, the system will recommend a new generic name drug production.

A flow diagram of the system is shown in Figure 3. The first step is the process of getting the information of original drug. Next step is the process of getting the generic name drug production. The following is the evaluation of pharmaceutical equivalence between two drugs formulations. The last step is a process to display a recommendation of the generic name drug tablet production.

The details of the main processes are explained as follow;

5.1 Getting the Original Name Drug information

The expert system gets two parameter groups from user. The first parameter group is preformulation study of active ingredient (drug) such as name, physicochemical properties, and weight in formulation. The second parameter group is properties of original drug product such as weight of tablet, disintegration time and dissolution profile as showed in Figure 4.

5.2 Recommending the Generic Name Drug Production

If user inputs only the informaiton of the original name drug formulation, the system will use only preformulation study of active ingredient and the parameters of the original product in recommending a production of generic name drug.

If user input the informaiton of the original name drug formulation and a generic name drug production, the system will focus on two main

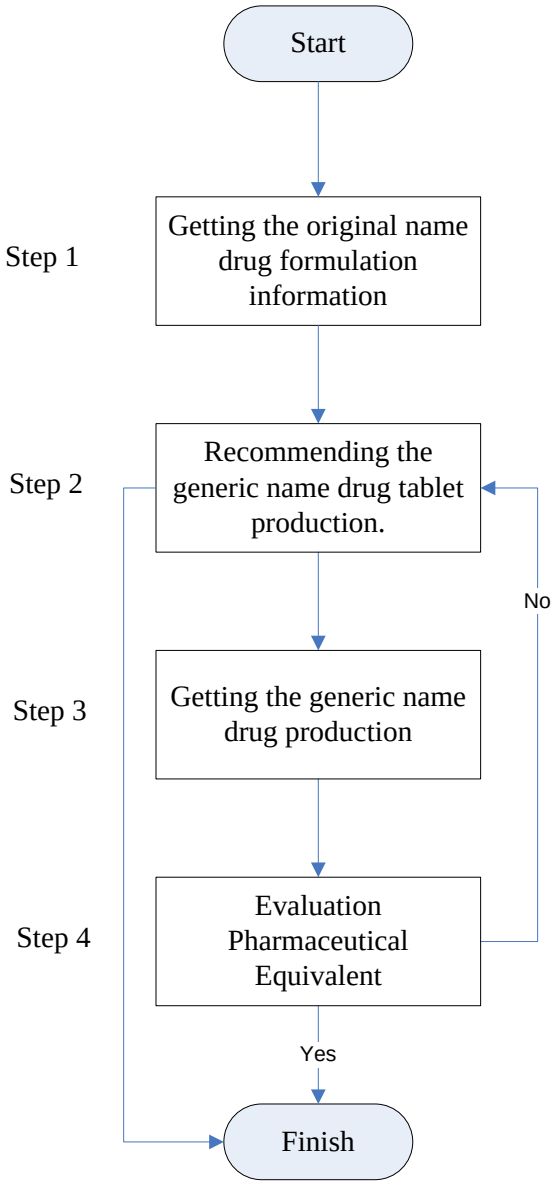

Figure 3. Flow diagram of the expert system of generic name drug production

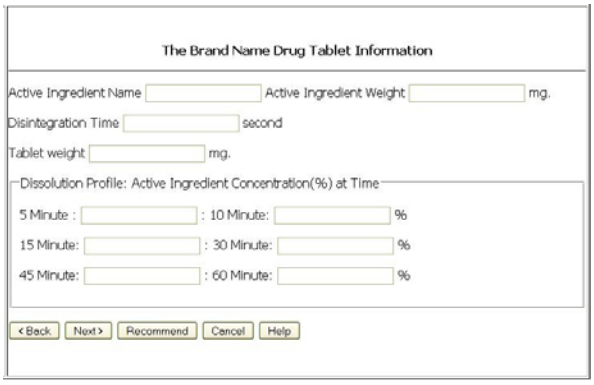

Figure 4. The screen of brand name drug information

points in recommending the generic drug. The first point, disintegration time is considered with friability. The disintegration time of generic drug is adjusted between 90-110% of disintegration time of the original drug. Modifying concentration of binder and disintegrant is the first strategy of adjusting disintegration time. If the disintegration time cannot be adjusted in range, it has to be modified at unit operations or changed to other excipients.

The second point, difference factor (f_1) and similarity factor (f_2) are considered. Strategies which adjust the f_1 values range between 0 and 15 and f_2 values range between 50 and 100 are modifing concentrations of solubilizer or wetting agent, adding solubilizer, wetting in the generic drug formulation, increasing solubility of drug and modifing unit operations.

The output of the expert system is shown as Table 3.

5.3 Getting the Generic Name Drug Production

The system gets the generic drug production that consists of a list of ingredients and their quantity, a set of tablet manufacturing instructions in laboratory scale, general standard quality controls that follow USP requirements (e.g. friability,content uniformity), and specific formulation quality controls such as dissolution profile and disintegration time. Figure 5 displays the getting information of generic name drug.

5.4 Evaluation Pharmaceutical Equivalent

This process is to evaluate the pharmaceuticals equivalent between the original drug and the generic drug, quality controls of the generic drug, and manufacturing problems. There are three points to confirm pharmaceutical equivalent of generic drug formulation; (1) difference (f_1) and similarity (f_2) factors should be in range, (2) the generic drug formulation passes the standard quality controls following USP, and (3) manu-

Table 3. An example of generic drug production from the expert system

The Recommended Generic Name Drug Tablet Production	
List of ingredient	Quality(mg.)
Drug A	20
Sodium lauryl sulphate	4.8
Tween80	4.8
Croscarmellose Sodium	7.2
Calcium Carbonate	48
Microcrystalline Cellulose	84
Lactose	68.8
Magnesium Stearate	2.4
Tablet weight	240
Instructions	
1. Dry mixed between Drug A and Sodium lauryl sulphate	
2. next, Wet mixed with Tween80	
3. next, Dry mixed with Calcium Carbonate	
4. next, Dry mixed with Microcrystalline Cellulose	
5. next, Dry mixed with Lactose	
6. next, Wet mixed with 95% Alcohol	
6. next, Size reduce by Sieve number 14	
7. next, Drying at 50 °C 5 Hours	
8. next, Size reduce by Sieve number 18	
9. next, Dry mixed with Croscarmellose Sodium	
10. next, Dry mixed with Magnesium Stearate	
11. Last, Compress at strength 9 kg.	

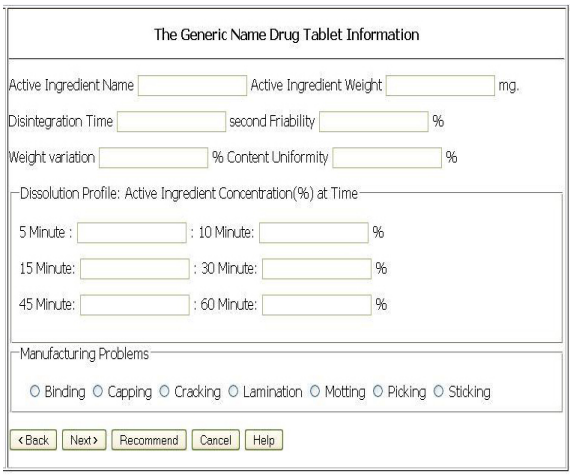

Figure 5. The screen of generic name drug information

facturing problems are false.

The difference factor (f_1) is a measurement of the relative error between the generic drug formulation curve and the trade name drug formulation curve, whereas the similarity factor (f_2) is the measurement of the similarity of the percent (%) dissolution between the generic drug formulation curve and the trade name drug formulation curve. Difference (f_1) and similarity (f_2) factors should be determined by performing the requisite dissolution rate testing on 12 units of each according to the FDA's Guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Form. (Shargel L. and Kanfer I., 2005) If the f_1 values range between 0 and 15 and f_2 values range between 50 and 100 the dissolution curves being compared are considered similar or equivalent. The closer f_1 and f_2 are to 0 and 100, respectively, the better the comparability of the curves.

These factors can be determined using the following formulae:

$$f_1 = \left\{ \frac{\left[\sum |R_t - T_t|\right]}{\left[\sum R_t\right]} 100 \right\}$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{I}{n} \sum w_t (R_t - T_t)^2 \right]^{-0.5} 100 \right\}$$

Where: *f*=fit factor; *Rt* = reference assay at time *t* (percent dissolved); *Tt* = test assay at time *t* (percent dissolved); *n* = number of sample points; wt = weight at time *t* (optional); Σ = summation from *t* = 1 to *t* = *n*

5.5 An Example of Difference (f_1) and Similarity (f_2) Factors Calculation

An example of dissolution profiles of a brand name drug, a generic name drug, and the generic name drug-add solubilizer illustrated in Figure 4. Difference factors (f_1) and similarity factor (f_2) values shown in Table 4 are for the generic name drug and the generic name drug-add solubilizer relative to the brand name drug. It indicates that the generic name drug-add solubilizer is equivalent to the brand name drug.

6 Conclusion and Future Work

We developed an expert system for generic name drug in tablet dosage form. The system is able to recommend a production of generic name drug that consists of a list of ingredients, quantity and a set of manufacturing instructions. The generic name drug will be reformulated until it is

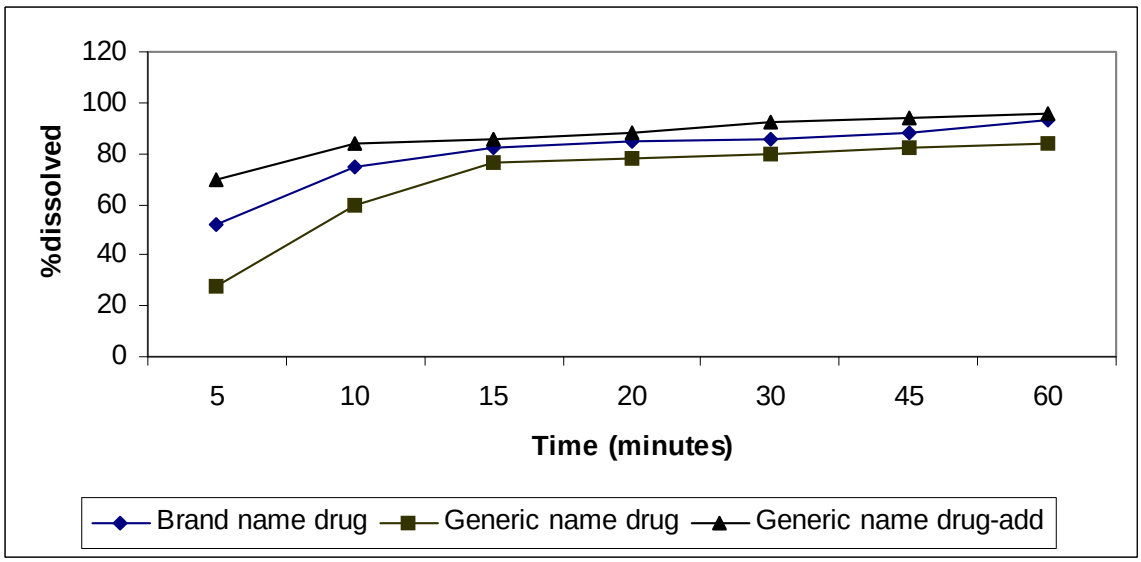

Figure 6. Dissolution profiles of examples of difference and similarity factors calculation

Table 3.Difference factors (f_1) and similarity factor (f_2) values of the generic name drug, and the generic name drug-add solubilizer relative to the brand name drug.

Factor	Generic name drug	Generic name drug-add solubilizer
f_1	13.01	8.73
f_2	45.64	53.27

pharmaceutical equivalence to the original drug. A domain knowledge which was built based on tablet production ontology consists of an excipients modelbase and a tablet productions modelbase. The domain knowledge is integrated with operation knowledge in production rules by JESS engine. Presently, there are fifteen rules which represented strategies in recommending the productin of the generic name drug.

In the future, we will add more the productions of generic name drug in the modelbases and apply the system to generic drug manufacturing factories.

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