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APPENDICES

APPENDIX A

- IF <Flowability of API is free flowing or good>
  AND <Compactability of API is good>
  AND <Temperature stability of API is stable or unstable>
  AND <Moisture stability of API is stable or unstable>
  AND <Percentage of API is more than 10%>
  THEN <Setting the process type as direct compression>
- IF <Flowability of API is free flowing or good or fair >
  AND <Compactability of API is good>
  AND <Temperature stability of API is stable or unstable>
  AND <Moisture stability of API is stable or unstable>
  AND <Percentage of API is more than 10%>
  THEN <Setting the process type as dry granulation>
- IF <Flowability of API is poor or very poor or extremely poor>
  AND <Compactability of API is poor or very poor>
  AND <Temperature stability of API is stable>
  AND <Moisture stability of API is stable>
  THEN <Setting the process type as wet granulation>
- IF <Disintegration time of original product is less than 180 seconds >
  AND <Disintegrant type is disintegrant>
  THEN <Setting disintegrant concentration as maximum>
- IF <Disintegration time of original product is less than 180 seconds >
  AND <Disintegrant type is super disintegrant>
  THEN <Setting disintegrant concentration as maximum >
- IF <Disintegration time of original product is between 180 and 300 seconds >
  AND <Disintegrant type is disintegrant>
  THEN <Setting disintegrant concentration as maximum >
- IF <Disintegration time of original product is between 180 and 300 seconds >
  AND <Disintegrant type is super disintegrant>
  THEN < Setting disintegrant concentration as medium >
- IF <Disintegration time of original product is more than 300 seconds>
  AND <Disintegrant type is disintegrant>
  THEN <Setting disintegrant concentration as minimum >
- IF <Disintegration time of original product is more than 300 seconds>
  AND <Disintegrant type is super disintegrant>
  THEN <Setting disintegrant concentration as minimum>

- IF <Solubility of API is very soluble or freely soluble or soluble>
  THEN <Set concentration of Solubilizer as minimum>

- IF <Solubility of API is sparing soluble or slightly soluble or very slightly soluble or insoluble>
  THEN <Setting solubilizer concentration as maximum>
- IF <Solubility of API is very soluble or freely soluble or soluble >
  THEN <Setting concentration of wetting agent as minimum>
- IF <Solubility of API is sparing soluble or slightly soluble or very slightly soluble or insoluble >
  THEN <Setting concentration of wetting agent as maximum >
- IF <Process type is direct compression>
  AND <Solubility of API is very soluble or freely soluble or soluble >
  AND <Lubricant type is lubricant or antiadherent or glidant>
  THEN <Setting lubricant concentration as maximum>
- IF <Process type is direct compression>
  AND <Solubility of API is sparing soluble or slightly soluble or very slightly soluble or insoluble >
  AND <Lubricant type is lubricant or antiadherent or glidant >
  THEN < Setting lubricant concentration as minimum>
- IF <Process type is dry granulation>
  AND <Solubility of API is very soluble or freely soluble or soluble >
  AND <Lubricant type is lubricant or antiadherent or glidant >
  THEN < Setting lubricant concentration as maximum>
- IF <Process type is dry granulation >
  AND <Solubility of API is sparing soluble or slightly soluble or very slightly soluble or insoluble >
  AND <Lubricant type is lubricant or antiadherent or glidant >
  THEN < Setting lubricant concentration as minimum>
- IF <Process type is wet granulation>
  AND <Solubility of API is very soluble or freely soluble or soluble >
  AND <Lubricant type is lubricant or antiadherent or glidant >
  THEN < Setting lubricant concentration as minimum >
- IF <Process type is wet granulation >
  AND <Solubility of API is sparing soluble or slightly soluble or very slightly soluble or insoluble >
  AND <Lubricant type is lubricant or antiadherent or glidant >
  THEN < Setting lubricant concentration as minimum >
- IF <Hardness of original product is less than 2 kilogram>
  AND < Binder type is hardest-slow split or hardest-fast split >
  THEN <Setting binder concentration as minimum>

- IF <Hardness of original product is less than 2 kilogram >
  AND < Binder type is harder-slow split or harder-fast split >
  THEN <Setting binder concentration as minimum>
- IF <Hardness of original product is less than 2 kilogram >
  AND < Binder type is soft-slow split or soft-fast split >
  THEN <Setting binder concentration as minimum>
- IF <Hardness of original product is between 2 and 5 kilogram>
  AND < Binder type is hardest-slow split or hardest-fast split >
  THEN <Setting binder concentration as medium>
- IF <Hardness of original product is between 2 and 5 kilogram >
  AND < Binder type is harder-slow split or harder-fast split >
  THEN <Setting binder concentration as medium>
- IF <Hardness of original product is between 2 and 5 kilogram >
  AND <Binder type is soft-slow split or soft-fast split >
  THEN <Setting binder concentration as medium>
- IF <Hardness of original product is more than 5 kilogram>
  AND <Binder type is hardest-slow split or hardest-fast split >
  THEN <Setting binder concentration as maximum>
- IF <Hardness of original product is more than 5 kilogram >
  AND <Binder type is harder-slow split or harder-fast split >
  THEN <Setting binder concentration as maximum>
- IF <Hardness of original product is more than 5 kilogram >
  AND < Binder type is soft-slow split or soft-fast split >
  THEN <Setting binder concentration as maximum>
- IF <Antioxidant exists>
  THEN <Setting antioxidant concentration as medium>
- IF <Buffering exists>
  THEN < Setting buffering agent concentration as medium >
- IF < Favoring exists>
  THEN <Setting flavoring agent concentration as medium>
- IF <Preservative exists>
  THEN <Setting preservative concentration as medium>
- IF <Diluent exists>
  THEN <Fulfilling diluent concentration to tablet weight>

APPENDIX B

- IF <Disintegration time of generic tablet is less than 90% of Disintegration time of original tablet >
  AND <Disintegrant concentration is not at maximum >
  THEN <Setting disintegrant concentration as maximum>
- IF <Disintegration time of generic tablet is less than 90% of Disintegration time of original tablet >
  AND <Disintegrant concentration is at maximum >
  THEN <Setting binder concentration as minimum>
- IF <Disintegration time of generic tablet is more than 90% of Disintegration time of original tablet >
  AND <Disintegrant concentration is not at minimum >
  THEN <Setting disintegrant concentration as minimum>
- IF <Disintegration time of generic tablet is more than 90% of Disintegration time of original tablet >
  AND <Disintegrant concentration is at minimum >
  AND <Disintegrant type is super disintegrant >
  THEN <Changing disintegrant type and setting concentration as minimum>

- IF <Dissolution profile of generic tablet is less than 90% of Dissolution profile of original tablet >
  AND <Solubilizer concentration is not at maximum >
  THEN <Setting solubilizer concentration as maximum>
- IF <Dissolution profile of generic tablet is less than 90% of Dissolution profile of original tablet >
  AND <Solubilizer concentration is at maximum >
  THEN <Adding wetting agent and setting concentration as medium>
- IF <Dissolution profile of generic tablet is less than 90% of Dissolution profile of original tablet >
  AND <Solubilizer concentration is at maximum >
  AND <Wetting concentration is not at maximum>
  THEN <Setting wetting agent concentration as maximum>
- IF <Dissolution profile of generic tablet is more than 90% of Dissolution profile of original tablet >
  AND <Solubilizer concentration is not at minimum >
  THEN <Setting solubilizer concentration as minimum>

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Ontology Development for Pharmaceutical Tablet Production Expert System*

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***Abstract*-In this paper, we propose a tablet production ontology to support a generic drug tablet production expert system. The ontology is used to model the information about pharmaceutical tablet production that consist of a list of ingredients and its quantity, a set of instructions that explain how to manufacture tablet in laboratory scale, standard quality control that follow USP requirements, and equivalent quality controls (dissolution profile and disintegration time). It can reusable and sharable with others pharmaceutical dosage forms production such as capsule, cream, gel and injection.**

I. INTRODUCTION

Pharmaceutical formulation development is information and knowledge intensive process. The more powerful intelligent software system that manages and accesses all available scientific data for efficient decision making process becomes necessary. To support the activity and decision making task in the formulation development process, it requires a systematic integrated framework which is based on formal and explicit modeling of related information.[1] Various forms of knowledge structure such as decision tree, object, frame and production rules are used in many intelligent software systems. Although these systems have the same concept, it is difficult to reuse or share knowledge among them.

Ontology is a specification of a conceptualization. That is, it is a description of concepts and relationships that exists for an agent or a community of agents. Creating ontology for representing knowledge enable experts to separate domain knowledge from operational knowledge, analyze domain knowledge, explicit domain assumptions, provide common understanding of the information structure and developers to reuse and share domain knowledge [2]. The created ontology provides a reference domain model that both human and software shares the same concept. It can be applied for various purposes such as searching, guiding and so on[3].

We design a framework for developing a pharmaceutical tablet production expert system. We apply ontology to model the generic drug immediate release tablet production knowledge and represent its content in terms of classes, relations, attributes and instances. In this paper, ontology is developed by applying role concept.

II. BACKGROUND

Several expert systems have been developed by numbers of pharmaceutical companies and academic institutes [4]. 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 this area (Table 1). Knowledge structures in intelligence software systems can be represented in two groups: (1) decision tree and production, and (2) object, frame and production rules. All of them, tablet formulation is only represented by of a list of ingredient and its quantity as shown in Table 2. It does not represent a set of instructions that explain how to manufacture pharmaceutical product.

TABLE 1
PUBLISHED APPLICATIONS OF PHARMACEUTICAL PRODUCT FORMULATION EXPERT SYSTEM

Company/Institution	Knowledge Structure
Cadilar Laboratories(India)	Dicision table and production rules
Galenical Development System, Heidelberg	Objects, frames and production rules
University of London/Capsugel System	Decision tree and production rules
Sanofi System	Objects, frames and production rules
Zeneca systems	Objects, frames and production rules
Boot System	Objects, frames and production 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

III. SYSTEM ARCHITECTURE

The generic drug immediate release tablet production expert system framework is shown in Fig. 1. This framework is made

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up of modules of knowledge base, inference engine, user interface, and developer interface. It consists of domain knowledge of tablet recipes and operational knowledge of rules to recommend a reliable tablet production. First, tablet recipe information from user is initially collected. Next, expert system retrieves the tablet formulation that closed to the target formulation from database. Then, it applies rules represented in JESS engine to find the most appropriate tablet formulation that is equivalent to the target tablet formulation. We develop a tablet production ontology, an operational knowledge represented in rule to JESS based on concept in ontology, and create tablet production instance that is exported in XML pattern in rational database system.

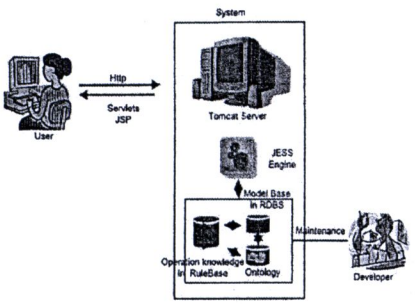

Figure 1. The Generic Drug Tablet Production Expert System Framework.

IV. ONTOLOGY BUILDING

In this section, pharmaceutical tablet production ontology (PTPO) is developed in Hozo[5], an ontology editor environment. The development of our ontology is based on the following steps.

A. Design classes

In PTPO, we define a tablet production class consists of the substance class which refers to main drug, the method class that is used in manufacturing tablet, a SQC class, an EQC class and a manufacturing problem class as shown in Figure 2.

Attribute stands for the specific characteristics of objects in any classes. There are two types of attribute: object type and data type. The data type attribute values are a primitive concept such as boolean, string, integer, and float. The object type attribute values are constraint class (es). For instance, hardness attribute is a specific characteristic in compression class. The value is float as shown in Figure 3.

B. Design class hierarchy

Class hierarchy represents is-a relation between classes. As shown in figure 3, method class which represents a sequence of processes in PTPO is divided to three types: Direct Compression (DC), and Granulation (G). Granulation can be classified into Wet granulation (WG), and Dry Granulation (DG). Processes in tablet manufacturing are composed of mixing, drying, communition and compression. Mixing is divided into two types: dry mixing and wet mixing.

C. Design role concept

In tablet formulation, excipients represent a chemical substance which assists formulating pharmaceutical tablet. A chemical substance which plays a role as excipient can be acted for many purposes. For example, microcrystalline cellulose is a substance which plays a role as excipient in formulating Drug X. It acts both as disintegrant, a particle separating, and binder, a cohesive particle binding.

Based on the behavior of excipients, we apply a role-concept tablet production class. Roles are sets of actions that are allowed for different purposes. Substances may be assigned one or more roles at the same time. Since any substances have their own concept, when a substance holds any roles, it will integrate between its concept and all role concepts that it acts. Union operation is applied in this case. Figure 4 illustrates an example of microcrystalline cellulose with two roles, disintegrant and binder.

D. Design specific relations

In tablet formulation, we need a fix order to control the sequence of processes. We define additional relation class; *precede* relation class *Precede* relation shows the ordering between two processes. It composes of two processes.

It is possible that there are two substances which is incompatible each other when formulating pharmaceutical tablet. For example, lactose and drug that has ammonium functional group can not exist together. Millard reaction effects tablet to change color, inactive because of malfunction. *Incompatiblewith* relation is defined to support incompatible situation. It composes of two substances.

Specific relation is applied to related class constraints in pharmaceutical tablet formulation. As shown in figure 4, precede relation shows that dry mixing_1 process comes before dry mixing_2 process.

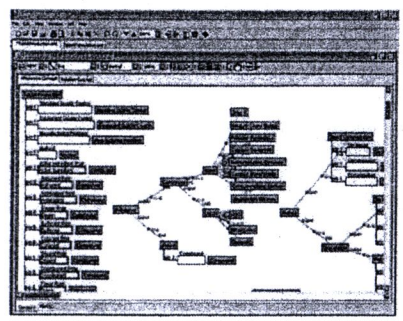

Figure 2. A Part-Role Concept in Tablet Production Class.

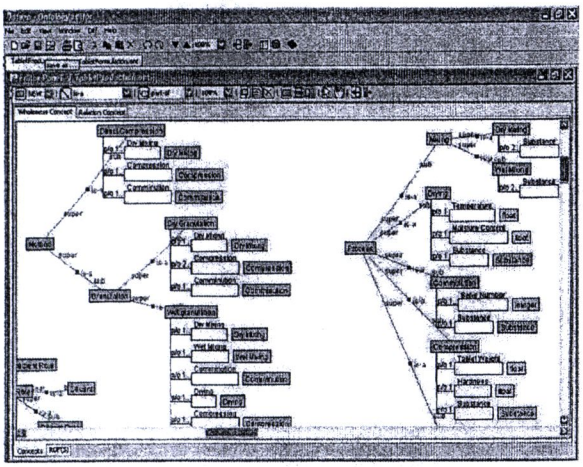

Figure 3. Defining class object type and data type

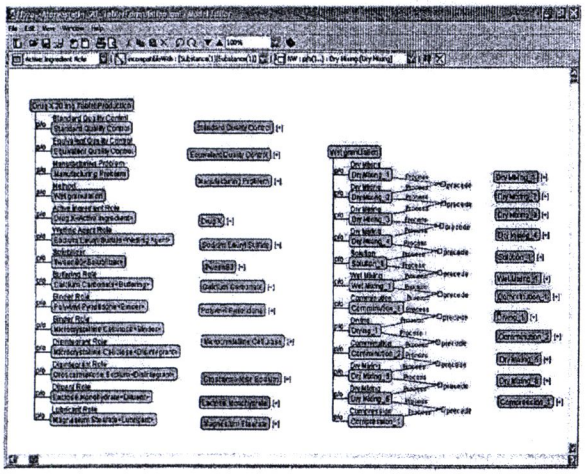

Figure 4. Tablet Production Instance

E. Instantiate object

After ontology is designed, object will be instantiated to apply in expert system by using Model Editor in Hozo environment. Figure 4 shows the tablet production instances that are built from tablet production ontology. With the limitation of space, all concept can not be displayed in figure 4. Table 3 represents all instance information which is related to figure 4.

V. Conclusion and Future Work

We developed tablet production ontology that covered a tablet recipe, QCs and manufacturing problems. The ontology is used for creating immediate release tablet production instances. Currently, there are forty one concepts are developed.

In the future, we will apply ontology to develop rules in JESS, and apply them in pharmaceutical tablet production expert system.

TABLE 3
INFORMATION OF EXAMPLE OF TABLET PRODUCTION INSTANCE

Tablet Production							
Tablet Recipe					QC and Manufacturing Problems		
Tablet Formulation			Method				
Substance	Quantity	Role	Process Name	Process Details			
Drug X	23 mg.	Active Ingredient	Dry Mixing_1	Dry mix between Drug X and Sodium Lauryl Sulfate(Mixture1)	SQC	Friability	0.5%
Sodium Lauryl Sulfate	3 mg.	Wetting Agent	Dry Mixing_2	Dry mix between Mixture1 and Calcium Carbonate(Mixture2)		Weight Variation	2%
Tween80	4.5 mg.	Solubilizer	Dry Mixing_3	Dry mix between Mixture2 and Microcrystalline Cellulose (Mixture3)		Content Uniformity	3%
Calcium Carbonate	72 mg.	Buffering Agent	Dry Mixing_4	Dry mix between Mixture3 and Lactose Monohydrate (Mixture4)	EQC	Disintegration Time	0.8 Minute
Polyvinyl Pyrrolidone	1.5 mg.	Binder	Solution1	Solute Polyvinyl Pyrrolidone and Tween80 in Water and Ethyl Alcohol(Mixture5)		Dissolution Profile	78.12,84.64, 92.11,94.78, 97.36,99.4
Microcrystalline Cellulose	90 mg.	Binder and Disintegrant	Wet Mixing_1	Wet mix between Mixture4 and Mixture5 (Mixture6)	Manufacturing Problem	All types of problem are false.	
Croscarmellose Sodium	15 mg.	Disintegrant	Comminution_1	Sieve Mixture6 through Mesh No. 20			
Lactose Monohydrate	89.5 mg.	Diluent	Drying_1	Make Mixture6 to dry at 50 °C until it has moisture content 0.8%			
Magnesium Stearate	1.5 mg.	Lubricant	Comminution_2	Sieve Mixture6 through Mesh No. 40)			
			Dry Mixing_5	Dry mix between Mixture6 and Croscarmellose Sodium (Mixture7)			
			Dry Mixing_6	Dry mix between Mixture7 and Magnesium Stearate (Mixture8)			
			Compression_1	Compress Mixture7, Hardness 7 kg. and weight 300 mg.			

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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

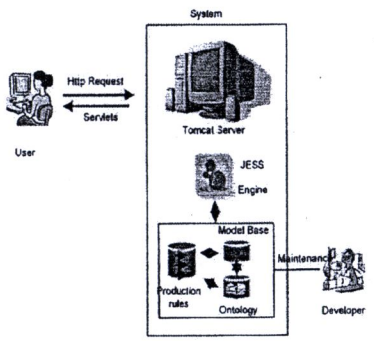

Figure 1. The Generic Drug Tablet Production Expert System Framework

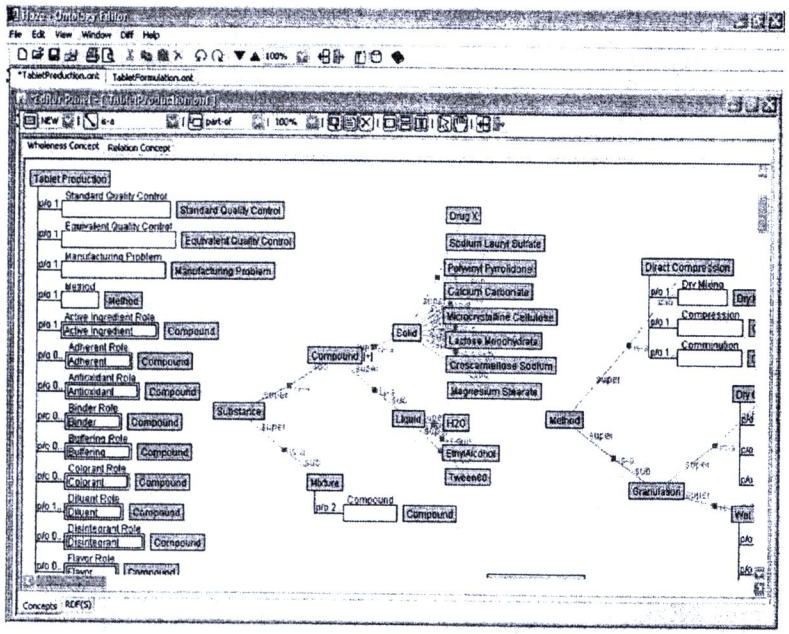

Figure 2. The Tablet Production Ontology

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

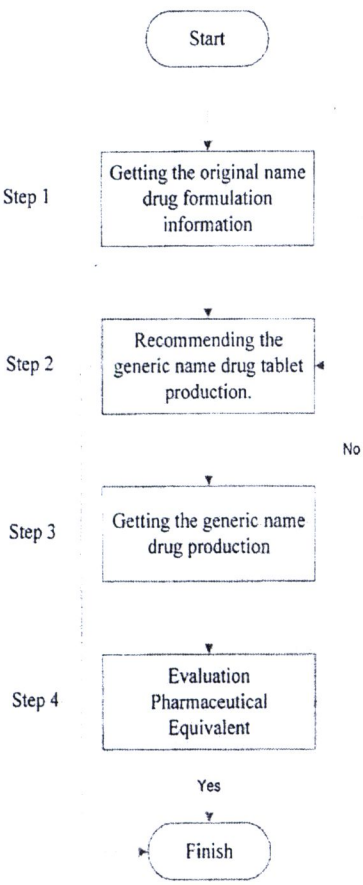

Figure 3. Flow diagram of the expert system of generic name drug production

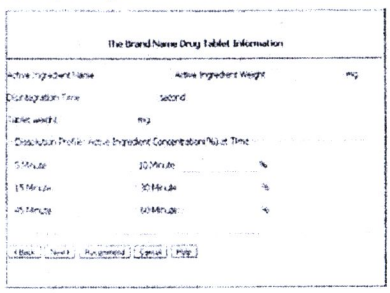

Figure 4. The screen of brand name drug information

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.	

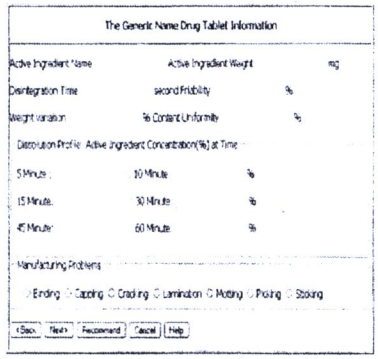

Figure 5. The screen of generic name drug information

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:

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

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

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

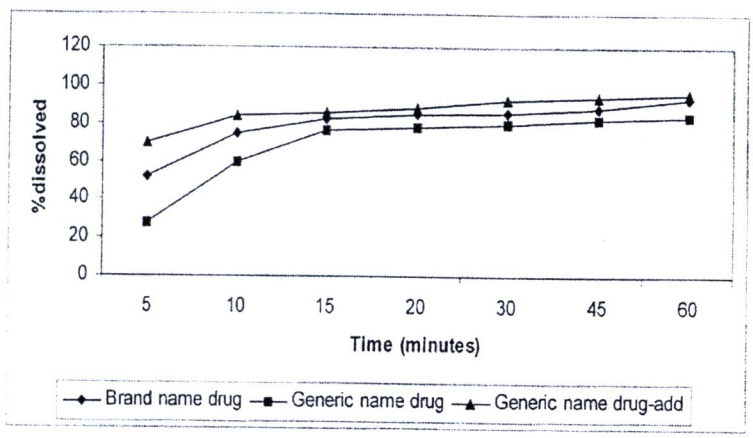

Figure 6. Dissolution profiles of examples of difference and similarity factors calculation

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.

Acknowledgment

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Paper

A Framework of Ontology-based Tablet Production Supporting System for a Drug Reformulation

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SUMMARY This paper presents a framework of supporting system for a drug formulation. We designed ontology to represent the related knowledge for reusable and sharing purposes. The designed ontology is applied with operation rules to suggest an appropriate generic drug production based on information of original drug. The system also provides a validation module to preliminarily approve a pharmaceutical equivalence of the suggested result. Preliminary testing with four random samples shows potential to reformulate a generic product by returning a satisfactory and acceptable of the system suggestions for all samples.

key words: Ontology, Generic drug production, Tablet Production Supporting System, Drug formulation

1. Introduction

Generally, a new invented original drug is legally protected from imitation by its patent. Once a patent of an original drug is expired, a generic version of the drug can be instantly developed by other drug companies. Normally, a cost of generic products is particularly lower than the market price of the original brand-name products since the generic production does not involve in an investment in a drug discovery and a full clinical test standard. With its low cost, a generic drug product becomes a demanded product in pharmaceutical market for daily usage. In fact, a generic drug is reformulated based on the details given in the original drug patent. Five years are generally consumed in a generic drug development. Especially, a laboratory development phase consumes around 25% from the entire development cycle [1]. Time consuming in a laboratory development phase is caused by implicit details in an original drug patent. The implicit information includes a crystal form of ingredients, an amount of excipients and a functional type of excipients. Moreover, a necessary factor in a generic drug reformulation certainly is a pharmaceutical equivalence between a generic drug and an original drug. In laboratory evaluation, it is mainly focused in generic drug development to primarily control a generic drug quality.

Despite many dosage forms of drug, tablet is the most preferred and widely used dosage form among other because of its stability, long life measured in years, easiness of transportation, and simple consumption. Moreover, a tablet dosage form covers over 80% of drug market [2]. Hence, this research focuses on a production of generic tablet formulation. One question raised in this research is *how to reformulate a generic tablet based on information given in an original drug patent effectively.*

A generic tablet reformulation is a re-engineering process using only information of an active ingredient, excipients and characteristics of the original product [3]. It is fundamental to define an explicit knowledge related to tablet production. An ontology is exploited to represent knowledge of a pharmaceutical tablet production. It is a backbone of knowledge that emulates expert thought to solve generic reformulation problems instead of human experts.

Unfortunately, none of existing expert systems in pharmaceutical field supports a generic drug production. In this paper, we purpose the first supporting system using an ontology knowledge base for a generic tablet reformulation. The system provides a suggestion of a certain amount of ingredients and manufacturing process including a set of sequent instructions. The contribution of the purposed system is not only suitable for a tablet reformulation, but also supports a general idea of a drug production in any pharmaceutical dosage form even herbal drug production by simply changing the related knowledge.

The structure of this paper is organized as follows. Section 2 describes a background of previous systems. Section 3 explains the pharmaceutical tablet production ontology and its related production rule. Section 4 defines our system architecture. An evaluation of the system is explained in detail in Section 5. Lastly, section 6 concludes the paper and indicates future works.

2. Background

Several supporting systems have been implemented in formulating a pharmaceutical product since 1989. They are categorized into two groups based on knowledge representation, namely production rule based system and frame based system.

2.1 Production rule based system

This group of systems represents their pharmaceutical knowledge within production rules. The production rules are conditional statements that specify actions to be taken or advice if a certain condition is true. There are

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two types of rules, atomic rules and composite rules. Atomic rule is a simple rule in if-then form. Atomic rules can be integrated together into composite rules, which are a more complex form with multiple conditions and actions. Since there is much knowledge used in a pharmaceutical product development, such as properties of drugs, properties of excipients, incompatibility between ingredients in formulations, and manufacturing processes, production rules become sophisticated. Furthermore, the more rules are defined, the more difficult on handling conflicts among rules will be executed. There are several examples in this group, such as Cadila system and Capsugel system. The Cadila system [4] has been developed to formulate drug tablets based on drug's physical, chemical and biological interrelated properties. The Capsugel system [5] has been implemented to aid the formulation of hard gelatin capsules. It was developed based on a statistical design, information of excipients and a database of marketed formulation. Both systems return outputs in term of ingredient list and their amount. These systems apply rules with information from the database. In fact, they are easy for development, but it cannot handle relations among knowledge in the deep level. In addition, the designed rules are specific for their purposes and they are hardly applied to another application.

2.2 Frame based system

Unlike the above systems, pharmaceutical knowledge of these systems is particularly separated from production rules and their knowledge is represented in frames. Frame is a structure that represents knowledge in a limited aspect of objects. With the use of frame representation, knowledge in pharmaceutical product development can be represented in a deeper level. Systems in this group include Galenical, Sanofi, Zeneca, and Boots. The Galenical system [6] has been designed to assist the development of a lot of formulations (e.g. aerosols, tablets, capsules, and intravenous injection), using chemical and physical properties of an active ingredient. The output of this system includes 1) formulation 2) production method 3) recommended packaging and 4) prediction of production properties. The Sanofi system [7] has been developed for formulating hard gelatin capsules based on preformulation study (a study on prior knowledge for the active ingredient). The Zeneca system [8] has been designed for formulating tablets, parenterals and film coatings. The Boots [9] system has been implemented to assist the formulation of sun oils, creams and lotions. It is obvious that a frame representation can be applied to several formulation types compared to the first group. Since knowledge represented in frame is restricted to slots which represent concepts in detail, it affects the simpler and clearer production rules.

From those aforementioned systems, their results provide only a list of excipients, their amount, and some attributes of productions such as the capsule size and the tablet diameter. This information alone is not sufficient for inexperienced pharmacists to effectively produce a generic drug since they additionally need production instructions in details in real drug production. Moreover, the systems have been all implemented for the creation of new drugs which have different criteria for drug validation. Therefore, they can scarcely be applied to a generic drug development.

Since the frame representation approach has expressive limits about contiguous relations for deep knowledge, it cannot handle relations among concepts properly. Normally, it is difficult to manage explicit complex relations separated from the frame. For example, an excipient in a drug formulation has a limited range of minimum and maximum concentration based on its function in the formulation. If the concentration of an excipient is lower or greater, the excipient will function in another manner or will possibly become malfunction. These conditions lead to formulation complexity and incomplete formulation issue respectively. Moreover, an incompatibility between two or more compounds is also a limitation of a frame representation. An incompatibility issue becomes much more complicate when two ingredients are mixed and turn incompatible to other ingredients which they are used to be compatible with. In the frame representation, a slot of a frame cannot handle and express these complex conditions sufficiently. In addition, the sequential instructions for tablet production cannot be simply achieved with information in a slot nor a usual relational schema.

Regarding complex deep knowledge in pharmaceutical generic tablet reformulation and production, our framework is designed based on ontology, which is apparently beyond the limitation of a usual relational schema and a frame representation in terms of hierarchical relation and additional complex relation between concepts. Our designed ontology is a knowledge base that completely draws on pharmaceutical domain knowledge of human expert. It also enables us to share and reuse knowledge in the system or across systems effectively.

3. Ontology-based Knowledge development

We use ontology to represent knowledge for its explicit specification of a shared conceptualization. To separate between declarative and procedural knowledge, we divide knowledge into two types: the domain knowledge and the operation knowledge. The domain knowledge is a declarative knowledge which is represented in ontology. The operation knowledge is a procedural knowledge which is represented in production rule.

3.1 Design of Domain knowledge

There are two main knowledge types in the domain knowledge: the general knowledge and the specific knowledge. The general knowledge is knowledge of tablet excipients which explains their properties, possible operation and manufacture suitable for them and drug formulation composition. We design this knowledge following the Handbook of Pharmaceutical Excipients [10]. The specific knowledge focuses on the original tablet formulation which is generated from literature and patent reviewing. It includes a list of the original tablet ingredients without any property and incompatibility and stability of an active ingredient in the formulation.

3.1.1 The Design of Pharmaceutical Tablet Production Ontology

A pharmaceutical tablet production ontology (PTPO) [11] is created by using an ontology editor called Hozo Environment [12]. The PTPO development process [13] is based on the following steps.

A. Design Classes

In PTPO, a tablet production class represents the definition of drug formulations. It consists of an active ingredient, excipients, formulation processes, a standard quality control (SQC), an equivalent quality control (EQC) and a caution.
The *main drug class* contains data of an active ingredient in tablet formulation. The *excipient class* provides data of other inactive ingredients which play a role in constructing a quality tablet, such as binder, diluent, disintegrant, and so on. The *process class* represents all activities used in manufacturing tablet. The *standard quality control* class is drug-independent quality controls used for validation a tablet quality based on United State Pharmacopeia standard, such as, weight variation, friability and content uniformity. The *equivalent quality control* (EQC) class is drug-dependent quality controls which are applied to validate between the original tablet and the produced generic tablet such as a dissolution profile. Lastly, the *caution class* is a class that represents problems in the experimental process. It reminds the pharmacist who reformulates the new drug alternatives about production process problems, such as binding, sticking and lamination.

B. Design Class Hierarchy

A class hierarchy is designed to identify the organized hierarchical structure among concepts in the tablet production. The relation of class hierarchy shows *is-a* relation to identify a subsumption relation. For example in Fig.1, the *process class* represents a sequence of unit operations in PTPO. It explains that the manufacturing process is a generalization of a granulation process[1] (G) and a direct compression process[2] (DC). In deeper level, a granulation process can be classified into a wet granulation (WG), and a dry granulation (DG). Another example of a class hierarchy is the *unit operations class*. It represents the fundamental methods using in the tablet production which can be divided into four main methods: mixing, drying, communition, and compression.

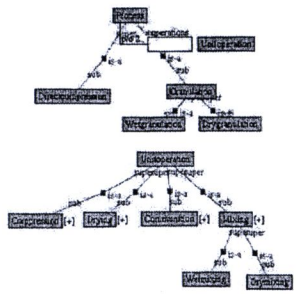

Fig.1 An example of class hierarchy.

C. Design Role Concept

In the tablet formulation, the excipients represent chemical substances which assist on formulating pharmaceutical tablets. One excipient can be functioned in many purposes based on its concentration. In different formulations, a role of the same excipient can vary depending on the purpose. We apply a role-concept *tablet production class* to handle this complexity. Roles are sets of actions that allow for multiple purposes. Basically, the excipients have their own concepts of possible roles. When they are selected in tablet formulation, their role are fixed based on the domain knowledge previously assigned by experts.

D. Design Additional Relations

Since we aim at defining a strong explicit relation, we solely concentrate on an *is-a* relation, a *part-of* relation and a *role concept*. However, in the tablet formulation, we need a strict order of unit operations to control their sequences. Additional relations are required to explicitly declare a sequence of unit operations. They are designed as additional relation classes, such as *precede relation* class which defines the order of two unit operations. In some cases, two excipients are incompatible between them when formulated together in pharmaceutical tablet. *Incompatiblewith* relation is designed to constrain the related classes in the pharmaceutical tablet formulation.

[1] A granulation is a process of using a liquid binder or lightly compaction to agglomerate the powder mixture before it is compressed as tablets.

[2] A direct compression is a process that does not require an initial method to compress the powder.

It is defined to support incompatible situations between two excipients. For example, the Millard reaction is the reaction in lactose that affects tablet to change its color and become inactive because of malfunction in a main drug with ammonium functional group. Additional relations are represented in term of relation class which experts can define individually apart from the fundamental relations, such as *is-a* relation or *part-of* relation.
The PTPO currently has six main classes, 126 subclass, five relations and ten role-concepts in total.

3.1.2 Instantiation of Pharmaceutical Tablet Ontology

After the ontology is created, the excipients and the tablet productions are instantiated by experts. They are represented in OWL-Lite instead of RDF since an RDF only provides a content data model for representing the basic elements for making simple statements about resources [14] and it is not suitable for complex semantic expression of the PTPO. For example, *is-a*, *part-of*, *precede* relations among classes in PTPO cannot be expressed in RDF. There are two methods for instantiation, mapping from database into ontology instance and instantiating manually using Instance Editor from Hozo environment. The former is suitable for developing formulation which data already exist whereas the latter is appropriate for a new instance creation. An example of the tablet production instances developed in Hozo environment is shown in Fig 2.

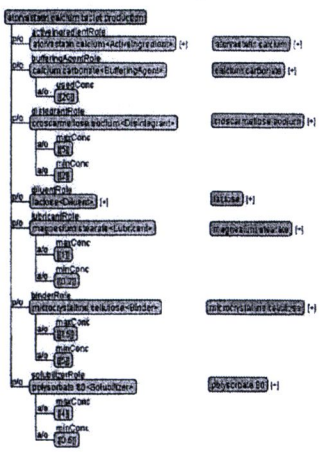

Fig. 2 An example of Atorvastatin Calcium instances.

3.2 Design of Operation knowledge

The operation knowledge is represented as production rules. They are collected from experience of experts and generic tablet formulation experiments. The operation knowledge is designed to formulate the generic name drug tablet based on; (1) an active ingredient's preformulation study such as physiochemical properties and (2) characteristics of an original drug tablet such as disintegration time and dissolution profile. The components of production rules are represented in the following form:

IF <condition(s)> THEN <action>.

When the <condition(s)> is triggered, the <action> will be executed. Fifty six production rules are employed in the present version.

4. System Architecture

As shown in Fig 3, our framework is designed to assist pharmacists to generate a tablet production of generic drug. The necessary data from PTPO (A), instances (B), and production rules (C) are processed in JESS inference engine [15]. They form the system knowledge base to effectively recommend a solution in our framework. The tablet production system consists of four modules.

1. Amount adjustment module (D)
2. Excipients modification module (E)
3. Process generation module (F)
4. Pharmaceutical validation module (G)

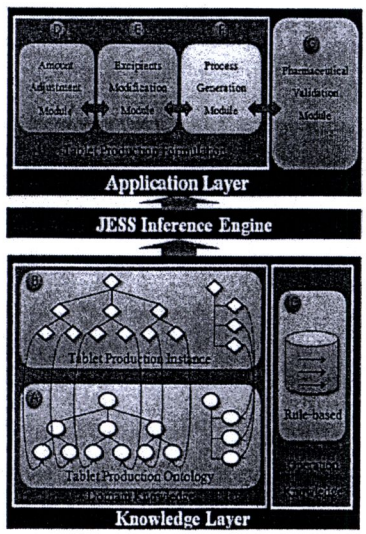

Fig. 3 A framework of the system.

4.1 Amount Adjustment Module

Based on ingredients declared in a patent, the system

adjusts the most suitable percentage amount per tablet of each excipient to suggest a generic drug production. An appropriate amount of the excipients are calculated based on their function in tablet formulation. The dissolution profile and integration time are also applied in rules if they are inputted into the system. The appropriate amount has to be set within the range between minimum and maximum value.

4.2 Excipients Modification Module

Normally, a patent gives us the information of main drug and all excipients. The formulation provided by the system will not modify excipients but only specify amount of them. However, since there are various types of each excipient, it is possible to apply different types when comparing to the information from a patent. The objective of this module is to modify excipients if the given ingredients cannot reformulate the appropriate tablet production of generic drug because of limitation of excipient amount range. Modifying excipients is a strategy to be applied together with the *amount adjustment module*, and propose a new generic drug formulation. Modifying strategies are adding and substitution depending on role of the focusing excipient. Whenever the new ingredients are determined, amounts of all excipients have to be re-calculated in amount by the *adjustment module*.

4.3 Process Generation Module

This module is designed to generate a set of production instructions from the given excipients and their amount value. The process is determined from physicochemical properties of drug and characteristics of tablet.

4.4 Pharmaceutical Validation Module

This module is designed to evaluate the pharmaceutical equivalence between the standard quality of original drug and the experimental quality result of the inputted generic drug. Difference (f_1) and Similarity (f_2) factors are determined by performing the requisite dissolution rate testing on twelve tablets according to the FDA's Guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Form [16]. 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 dissolution curve between the generic drug and the trade name drug. If the f_1 values range between 0 and 15 and f_2 values range between 50 and 100, both dissolution curves are compared. The range of similarity of f_1 and f_2 is set up between 0 and 100. The validated generic drug tablet is satisfactory unless the curve reaches over the acceptable range. These factors can be determined using the following equations [16]:

$$f_1 = \left\{\frac{[\sum|R_t - T_t|]}{[\sum R_t]} 100\right\} \quad (1)$$

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

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

5. Evaluation

To evaluate the system, four original drugs are randomly selected as representative samples based on the active ingredient (API) criteria. The first criterion is a solubility of API. Solubility can be categorized into two groups. *A1* refers to a group of a tablet that contains very soluble, freely soluble or soluble API whereas *A2* denotes to a group of a tablet that contains sparing soluble, slightly soluble, very slightly soluble or practically insoluble API. The second criterion is a dose and ratio of API. A percentage amount of an active ingredient is classified into two types. *B1* indicates a group of a tablet that its API is lower than 25% from the total dose whereas *B2* designates a tablet that its API is over 25% from the total dose. These two factors are focused to certainly cover all different issues of generic tablet production. The four representatives are shown in Table 1.

Table. 1 Four sample tablets for evaluation.

		Dose and ratio of active ingredient	
		B1	B2
Solubility of active ingredient	A1	Metformin Hydrochloride	Hydroxyzine Hydrochloride
	A2	Paracetamol	Atorvastatin Calcium

Based on the validation criteria mentioned in Section 4.4, the generic products of metformin hydrochloride, paracetamol and hydroxyzine hydrochloride produced regarding the system suggestion are all acceptable from the first suggestion. For the generic products of atorvastatin calcium, they are not pharmaceutically equivalent for the first trial. The system; therefore, executed the *excipients modification module* and gave the pharmaceutically equivalent formulation and production in the later attempt. To explain a process and related knowledge used in the system, the case of the atorvastatin calcium is exemplified in detail since all modules of the system was applied before the suggestions were satisfactory. In the system, a work flow process are separated into four processes, 1) preliminary process, 2) generic drug tablet reformulation process, 3) laboratorial production process, and 4) pharmaceutical equivalence validation process.

A preliminary process is a process for users to gather

information from both a preformulation experiment of an original drug in laboratory and a patent reviewing. From a preformulation process in a laboratory, users acquire characteristics[3] of original drug tablet and properties of an active ingredient (API) such as flowability and compressibility. From an original drug patent reviewing, user gains a list of excipients, the active ingredient with its amount, and its properties such as solubility and stability [17]. In a preliminary process, the obtained information of the Atorvastatin Calcium and its active ingredient (API) is illustrated in Table 2.

Table. 2 The Atorvastatin Calcium information.

Information type	Value
Solubility	Very slight soluble
Flowability	Fair
Fracture surface	Rough
Temperature stability	Stable
Moisture stability	Stable
API weight	20 mg.
Tablet weight	300 mg.
Hardness	5.2 kg.
Disintegration Time	50 sec.
Dissolution profile (%) at a minute of 5/10/15/30/45/60	91.08/98.37/101.04/101.07/101.28/101.20
Ingredients [known amount]	• Atorvastatin calcium [20 mg.] • Calcium carbonate • Croscarmellose sodium • Microcrystalline cellulose • Lactose • Magnesium stearate • Polysorbate 80

A generic drug tablet reformulation is a process to generate a generic formulation based on the input from preliminary process. In this process, the system returns a generic drug production which includes all ingredients with their amount, manufacturing process and a set of instructions. For the atorvastatin calcium, the system generated the suggestion shown in Table 3.

The system sets up amount values of excipients at *amount adjustment module*. An amount of each ingredient is calculated from the given tablet characteristics and the properties of main drug. The calculation and adjustment are based on *operation knowledge*. An available amount range of each ingredient is informed in *domain knowledge*.

From the atorvastatin calcium case, the *operation knowledge* represented in the rules given in Table 4 was applied according to *domain knowledge* shown in Figure 2. For example, the microcrystalline cellulose which plays a binder role is set to maximum regarding the rule III. In addition, the manufacturing process of the atorvastatin calcium is set to a wet granulation because the condition of rule VII was triggered.

Table. 3 The suggestion for the generic atorvastatin calcium.

List of ingredients	Function	Weight
Atorvastatin calcium	Active ingredient	20.00 mg.
Calcium carbonate	Buffering agent	60.00 mg.
Croscarmellose sodium	Disintegrant	15.00 mg.
Microcrystalline cellulose	Binder	45.00 mg.
Magnesium stearate	Lubricant	0.60 mg.
Polysorbate 80	Solubilizer	12.00 mg.
Lactose	Diluent	147.40 mg.
Other suggestion	**Value**	
Manufacturing process	Wet granulation	
Instructions in order	1. Wet mixing API and solubilizer 2. Dry mixing the mixture from 1 with disinitegrant, binder, buffering agent and diluent. 3. Wet mixing the mixture from 2 with water until it wet. 4. Communition with sieve no.14 5. Drying 6. Communition with sieve no.18 7. Compression	

Table. 4 The rules used in the suggestion of the atorvastatin calcium.

Rule no.	Detail of rule
I	IF <buffering agent exists> THEN <set the concentration of buffering agent at normal concentration>
II	IF <disintegration time of the original is less than or equal 180 seconds> AND <type of disintegrant is super-disintegrant> THEN <set the concentration of disintegrant at maximum concentration>
III	IF <hardness of the original is more than 5 kg> AND <type of binder is hardest> THEN <set the concentration of binders at maximum concentration>
IV	IF <solubility of API is sparing soluble or slightly soluble or very slightly soluble or practically insoluble > THEN <set the concentration of lubricant at minimum concentration>
V	IF <solubility of API is sparing soluble, slightly soluble, very slightly soluble, or practically insoluble> THEN <set the concentration of solubilizer at maximum>
VI	IF <diluent exists> THEN <set diluent with the left amount>
VII	IF < API concentration is less than 10%> THEN < set the process type as Wet granulation >

[3] The characteristics of a tablet are a disintegration time of a tablet, a dissolution profile of a tablet, tablet hardness, a fragment surface, etc.

The formulation result is consequently transferred to *process generation module* to generate a set of instructions based on those values [18].

After the system returns a result, generic tablets were produced based on the suggestion in the laboratorial production process by pharmacists. The produced tablets were tested in quality controls by user in laboratory. The quality control results were filled in the system to calculate f_1 and f_2 score to validate its quality in a pharmaceutical equivalence validation process. Once the result of the produced drug is validated that it contains a pharmaceutical equivalence, the system process is terminated. For the atorvastatin calcium case, the quality control results of the generic based on the suggestion given in Table 3 are shown in Table 5.

Table. 5 The pharmaceutical equivalence result between the original and the generic atorvastatin calcium following system suggestion.

Dissolution profile (%) at a minute of 5/10/15/30/45/60/average		Disintegration Time (sec.)	
Original	Generic	Original	Generic
91.08	54.05	50	193
98.37	61.75	Pharmaceutical Equivalence	
101.04	64.25		
101.07	65.22	F_1	F_2
101.28	65.50	36.51	23.75
101.20	66.38	> (0-15)	< (50-100)
99.01	**62.86**	**Fail**	**Fail**

Since the result in Table 5 is unacceptable, the details from quality control and dissolution are utilized as additional information for an improvement of a later suggestion. To improve a suggestion, differences of an average dissolution profiles and disintegration time between original and generic products are focused. Both of the values of the generic product are not allowed to be below or over 10% of the original product.

In the example case, the average of dissolution profile of the generic version is over 10%. Moreover, the disintegration time of generic product also needs improvement since it also exceeds 10% of the disintegration time of the original product. To improve a suggestion, the rule I and II in table 6 are triggered to add a wetting agent to the formulation and to adjust a concentration of the binder, respectively. After the excipients and amounts were modified, the set of instruction were rebuilt accordingly. The modified suggestion of the atorvastatin calcium is shown in Table 7. The generic products were later produced following the given improved suggestion and they finally showed a pharmaceutical equivalence result. Table 8 illustrates the pharmaceutical equivalence result between the original and the improved generic atorvastatin calcium. Hence, the process was satisfactorily completed.

Table. 6 The improvement rules used in the atorvastatin calcium.

Rule no.	Detail of rule
I	IF <dissolution profile is over an acceptable range> AND <solubilizer is at maximun> AND <wetting agent does not exist> THEN <add wetting agent excipient with a half amount of existing solubilizer and decrease the amount of the existing solubizer to half>
II	IF <disintegration is over an acceptable range > AND <disintegrant is at maximun> AND <type of disintegrant is super-disintegrant> AND <another excipient has a possible role as disintegrant> THEN <set a concentration of the excipient that has a possible role as disintegrant to perform a role of disintegrant function>

Table. 7 The improved suggestion for the generic atorvastatin calcium.

List of ingredients	Function	Weight
Atorvastatin calcium	Active ingredient	20.00 mg.
Calcium carbonate	Buffering agent	60.00 mg.
Croscarmellose sodium	Disintegrant	15.00 mg.
Microcrystalline cellulose	Binder	**75.00 mg.**
Magnesium stearate	Lubricant	0.60 mg.
Polysorbate 80	Solubilizer	**6.00 mg.**
Sodium lauryl sulfate	**Wetting agent**	**6.00 mg.**
Lactose	Diluent	147.40 mg.
Other suggestion	**Value**	
Manufacturing process	Wet granulation	
Instructions in order	1. Wet mixing API and solubilizer 2. Dry mixing the mixture from 1 with disinitegrant, binder, buffering agent and diluent. 3. Wet mixing the mixture from 2 with water until it wet. 4. Communition with sieve no.14 5. Drying 6. Communition with sieve no.18 **7. Dry mixing mixture and magnesium stearate** 8. Compression	

Table. 8 The pharmaceutical equivalence result between the original products and the improved generic atorvastatin calcium.

Dissolution profile (%) at a minute of 5/10/15/30/45/60/average		Disintegration Time (sec.)	
Original	Generic	Original	Generic
91.08	89.81	50	46
98.37	100.86	Pharmaceutical Equivalence	
101.04	102.91		
101.07	102.86	F_1	F_2
101.28	103.06	1.93	84.29
101.20	103.45	= (0-15)	= (50-100)
99.01	100.49	Acceptable	Acceptable

7. Conclusion and Future Work

In this paper, we propose a framework of a pharmaceutical supporting system for generic tablet reformulation and production. An ontology is exploited to represent domain knowledge of excipients and tablet formulation from document, literature and patent reviews. Beside, production rules represent operation knowledge from experience of experts and generic drug tablet formulation experiments. The number of classes, relations, role-concepts and rules in the present version are one hundred twenty six, five, ten and fifty six, respectively. The system consists of four modules which are the amount adjustment module, the excipient modification module, the process generation module and the pharmaceutical validation module. The first three modules assist a user in generating a generic drug production. The pharmaceutical validation module facilitates the user to validate a pharmaceutical equivalence between the generic products following the suggestion of the system and the original products.

Based on the evaluation result, the system shows promising potential in term of successful reformulation of four random sampling original. Especially, three of them showed the pharmaceutical equivalence to their original products from the first recommendation.

In the future, we plan to develop a user-friendly interface for users to directly instantiate their excipient information and condition rule into the knowledge base. Moreover, we plan to improve the system for supporting an herbal tablet production which is a traditional product in a pharmaceutical market of several countries. Lastly, we also plan to adapt our system and ontology to other dosage forms such as capsule, liquid and powder.

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