CHAPTER 3

MATERIALS AND METHODS

The ontology-based expert system for a generic drug production of immediate release tablet (OXPIRT) is implemented to support a generic immediate release tablet formulation and production. Additional, this system also includes an ability to support a herbal tablet production. There are two types of pharmaceutical knowledge using in the system: domain knowledge and operation knowledge. The domain knowledge is a declarative knowledge represented in ontology. The operation knowledge is a procedural knowledge which is assigned in a form of production rules. OXPIRT uses ontology based domain knowledge for information and it makes a decision regarding to a set of given production rules. With little information of the tablet given in expired patent, inference engine is exploited to infer a result. For possibility of inference, the initial recommend output might not give a correct formulation, but the system takes the output as additional information to improve later result. OXPIRT consists of three parts: 1) ontology-based domain knowledge, 2) operation knowledge representing in production rules and 3) recommendation system.

3.1 Development of domain knowledge

For serving as knowledge for a tablet production, domain knowledge must be carefully crafted with all details including concept, type of concept, relation among concepts, role of concept, and instance. In this work, ontology is applied to represent the domain knowledge that is specific to a tablet production.

There are two main knowledge types in the domain knowledge: the general knowledge and the specific knowledge. The general knowledge is a knowledge of excipients which explains their properties, the stability and incompatibility among each other, possible methodology suitable for them and drug formulation composition. We design this knowledge based on Handbook of Pharmaceutical Excipients (Rowe et al., 2005). The specific knowledge is data of the specific drug retrieved from literature and patent reviewing. This knowledge includes the original formulation which provides a name of active ingredient with its amount, a list of excipients without any properties and amount of excipient in the formulation, and the incompatibility and stability of the drug. Additionally, a role for each excipient in specific knowledge is given by experience of an expert.

3.1.1 Design of Ontology

A pharmaceutical tablet production ontology (PTPO) is created by using an Ontology Editor called Hozo (Kozaki et al., 2002). There are three parts of design.

3.1.1.1 Class designing

In PTPO, a tablet production class represents the definition of drug formulations. It consists of main drug, excipients, formulation processes, a standard quality control (SQC), an equivalent quality control (EQC) and a caution.

Main drug class contains data of an active ingredient of drug formulation. Excipient class provides data of the combination of other ingredients which play a role in constructing a quality drug, such as binding ingredients, accelerating the reaction and so forth. Process class represents all actions and their order used in tablet

manufacturing. Standard quality control (SQC) class is drug-independent quality controls used for validation parameters of formulation based on United State Pharmacopeia standard. It includes weight variation, friability, content uniformity and so on. Equivalent quality control (EQC) class is drug-dependent quality controls which are applied to validate a quality between the original product and the generic product in term on their pharmaceutical equivalence, the dissolution profile for instance. Lastly, caution class is a class that represents problems occurred in the experimental process. It reminds the pharmacist who alternatively formulates the generic product about the possibility of cautious production problems, such as binding, sticking and lamination.

3.1.1.2 Relation designing

For any classes, they are linked to other classes and their attributes by assigning basic relation; 1) is-a; 2) part-of (p/o) and 3) attribute-of (a/o).

An *is-a* relation indicates a hierarchical relation of each class. An *is-a* relation is a relationship where one class A is a subclass of another class B (and so B is a superclass of A). A class hierarchy is designed to identify the hierarchical organized structure among concepts in the tablet formulation.

For example from Figure 3.1, the process class represents a sequence of unit operations in PTPO. It explains how to make a tablet, such as Granulation (G) and Direct Compression (DC). Granulation is a process of using a liquid binder or lightly compaction to agglomerate the powder mixture before it is compressed to be tablets whereas direct compression is a process that does not require method to compress the powder. Granulation can be classified into Wet Granulation (WG), and Dry

Granulation (DG). Another example of a class hierarchy is the *Unitoperation* class. It represents the fundamental methods using in the tablet production which can be divided into four main methods: mixing, drying, communition, and compression.

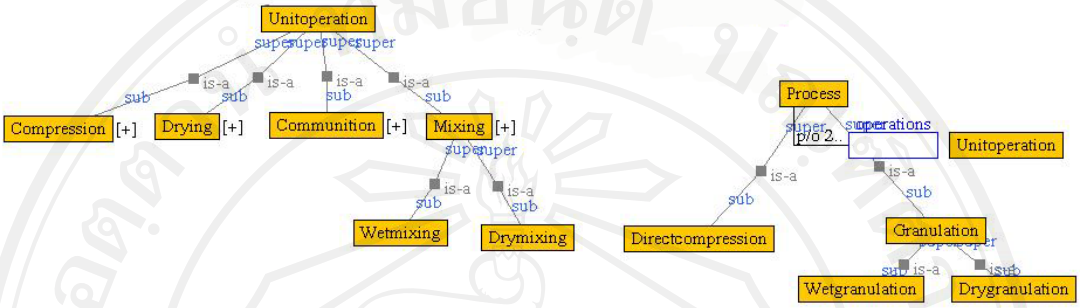

Figure 3.1 An example of a hierarchy

A *part-of* relation (p/o) is a relationship where one class A is a member of another class B. It is normally focused on the explanation of concept. For more information, multiple part-of relationships combine to form a possessive relation. For part-of relation, it is required to set a class constraint which limits a number of possible values for the class, called cardinality. Cardinality can be specific to a concrete number more than zero, number in range or least number. For instance from Figure 3.1, the *Unitoperation* class is a part of the process class which means any processes have two of any unit operations.

An *attribute-of* (a/o) is a relationship where one class has an attribute. In PTPO, attribute is a relation represented a specific property of class, where an instance is defined to a class.

Three above relations are basic relation used in several general ontologies. However, these are not sufficient for covering relation for pharmaceutical domain knowledge. In the tablet formulation, we need a strict order of unit operations to control their sequence. Additional relations are required to explicitly declare a

sequence of unit operations. They are designed as an additional relation class, such as precede relation class which defines the order of two unit operations. In some cases, two excipients are incompatible with each other when formulated together in pharmaceutical tablet. *Incompatiblewith* relation is designed to constrain the related class in the pharmaceutical tablet formulation. It is defined to support an incompatible situation between two excipients. For example, 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 fundamental relations, such as is-a relation or part-of relation.

3.1.1.3 Role concept designing

In the tablet formulation, the excipients represent chemical substances which assist on formulating pharmaceutical tablets. It can be functioned in many purposes. Based on the behavior of the excipients, we apply a role-concept tablet production class. Roles are sets of actions that allow any concepts function for multiple purposes. Basically, the excipients have their own concepts. When they hold many roles, we design to integrate between their concepts and all role concepts. To define one concept of excipient type, the compound in formulation is particularly considered for the role it plays. With the role, a compound is clearly indexed to a specific type of an excipient.

For example, microcrystalline cellulose can play two roles of an excipient type, disintegrant and binder. From Figure 3.2 A role concept of disintegrant, a compound that plays a role of causing a tablet to undergo fission or lose its particles

can be considered that it is a disintegrant. An example of a role concept in Hozo is illustrated in Figure 3.2.

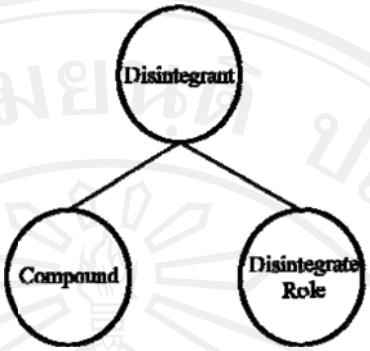

Figure 3.2 A role concept of disintegrant

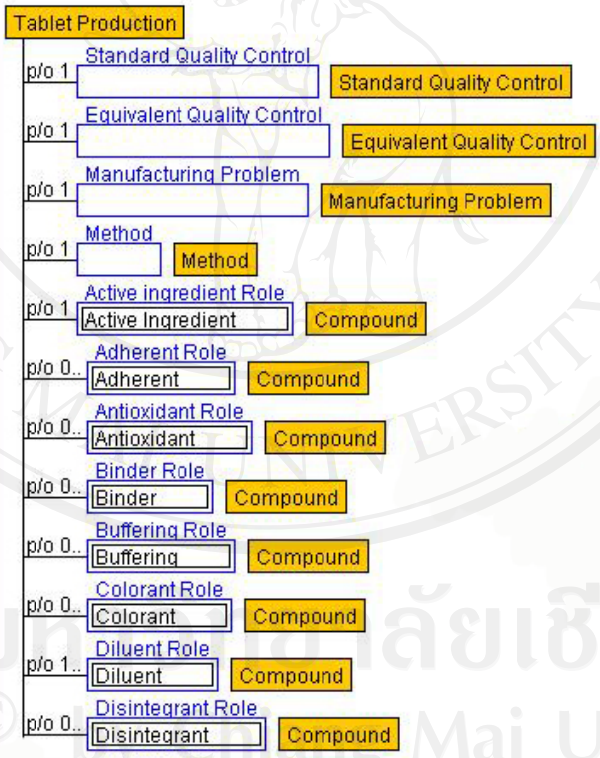

Figure 3.3 An example of a role concept

Upon the PTPO design, a statistic and a detail of class are shown in Table 3.1.

Table 3.1 A statistic and a detail of class in PTPO

	Main Objects	**Relations**	**Role concepts**
Total amount	6	5	10
Details	• Tablet production • Compound • Process • Unit operation • Manufacturing problem • Quality control	• *Is-a* relation • *Part-of* relation • *Attribute-of* relation • *Precede* relation • *Incompatiblewith* relation	• Active ingredient • Diluent • Binder • Disintegrant • Lubricant • Solubilizer • Antioxidant • Buffering agent • Preservative • Flavoring

3.1.2 Instantiation of Ontology

After the ontology is created, data of both the general knowledge and the specific knowledge are instantiated by expert into designed ontology. They are represented in OWL format. There are two methods for instantiation; 1) mapping from database into ontology instance and 2) handcrafted instantiation in Instance Editor by Hozo environment. The former is suitable for developing formulation which data already exist. The latter is appropriate for a new instance creation. For PTPO, instantiation is assigned manually by expert since there is no existing database for tablet production. An example of the tablet production instances developed by the tablet production ontology is shown in Figure 3.3.

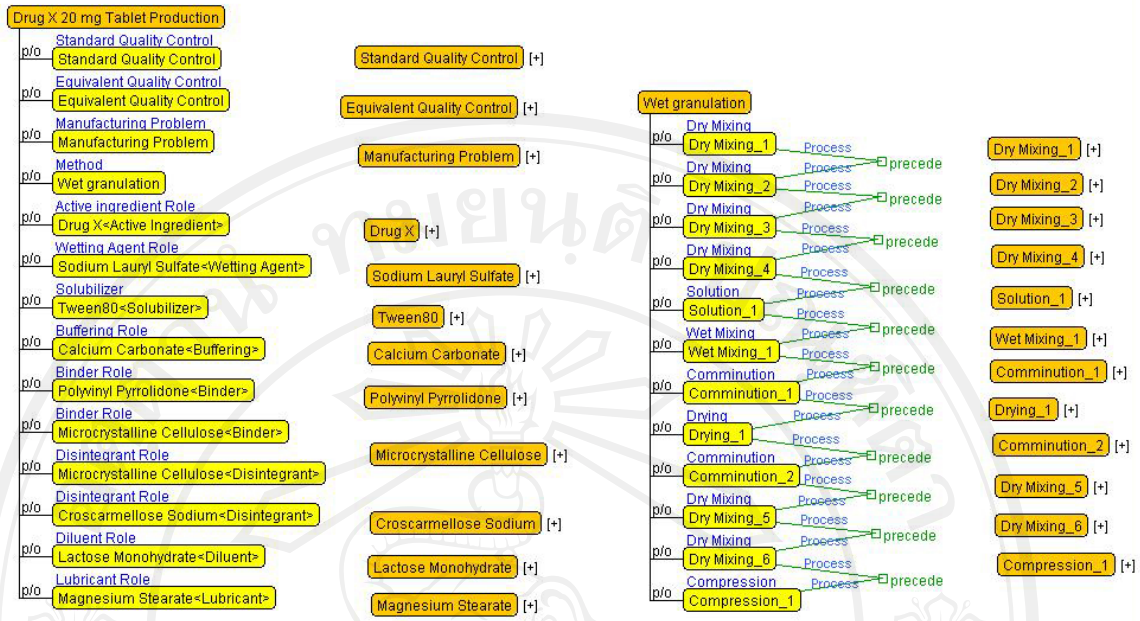

Figure 3.4 The instantiation of tablet production

3.2 Development of operation knowledge

Operation knowledge is a case based knowledge collected from experience of experts and generic drug tablet formulation experiments. In PTPO, operation knowledge is represented in a set of production rules. 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 characteristic of original product tablet such as disintegration time and dissolution profile. The components of production rules are represented in the form:

IF	<condition(s)>	THEN	<action>

When the <condition(s)> is triggered, the <action> will be executed.

In details, the production rules can be classified into two groups regarding to their criterion. The former is a set of rules which concerns a generation of new tablet production. In this group can be categorized into two subgroups which are for generic

table production and herbal tablet production. The latter is rules that modify and improve an error output to correct later recommended result.

For the rules of generating new tablet production, there are divided based on rule functions into ten types as shown in Table 3.2. For details in depth, all rules are provided in Appendix A.

Table 3.2 A set of rules of generating new production of tablet

Type of rule		Conditional Factor	Number of rules
Process		Percentage amount of API Flowability value between 0-5[1] Compactability value between 0-4[2] Temperature stability of API (yes or no) Moisture stability of API (yes or no)	3
Disintegrant		Disintegration time Disintegrant type (super disintegrant or disintegrant)	6
Solubilizer		Solubility value of API between 0-6[3]	2
Wetting agent		Solubility value of API between 0-6[3]	2
Lubricant		Process type (wet granulation, dry granulation or direct compression) Solubility value of API between 0-6[3] Lubricant type (Lubricant, Antiadherent or glidant)	6
Binder		Value of hardness Binder type(0a, 0b, 1a, 1b, 2a or 2b)[4]	9
Other excipients	Antioxidant Buffering agent Flavoring agent Preservative	Their own function factor within limited allowed range	4
Diluent		fulfillment	1
		Total	33

[1]Flowing value is as follows: 0=free, 1=good, 2=fair, 3=poor, 4=very poor, 5=extremely poor.
[2]Value of compactability is as follows: 0=good, 1=fair, 2=poor, 3=very poor, 4=extremely poor.
[3]Solubility value is as follows: 0=very soluble, 1=freely soluble, 2=soluble, 3=sparing soluble, 4=slight soluble, 5=very soluble, 6=practically insoluble.
[4]In the rule, 0=very hard, 1= hard, 2=weak, a=fast disintegration, and b=slow disintegration.

From the first output formulation, which fails to serve pharmaceutical equivalent, there are another set of rules that modifies and improves the output. These rules assist to fix the result in terms of 1) non-equivalent dissolution profile calculated by equation 1 given in Section 2.1; and 2) standard of quality control; for example, hardness and friability. These rules can be grouped into two types based on error category. They are illustrated in Table 3.3. More details of the rules that modify and improve the result are provided in Appendix B.

Table 3.3 A set of rules of improving incorrect result

Type of rule	Conditional Factor	Number of rules
Dissolution profile improvement	average concentration of two focused time points[5] in dissolution profile over 10% of disintegration time or less than 10% of disintegration time	4
Disintegration time improvement	over 1% of friability not in range of content uniformity standard not in range of weight variation standard	4
	Total	8

For non-equivalent dissolution profile, there are two points to improve it. First is to examine a disintegration time. If disintegration time is not in a specific acceptable range (10%), the disintegrant must be focused. The step to improve a next suggestion is given in Figure 3.5.

[5]There are two focused time points at 5 minute and 10 minute of dissolution profile.

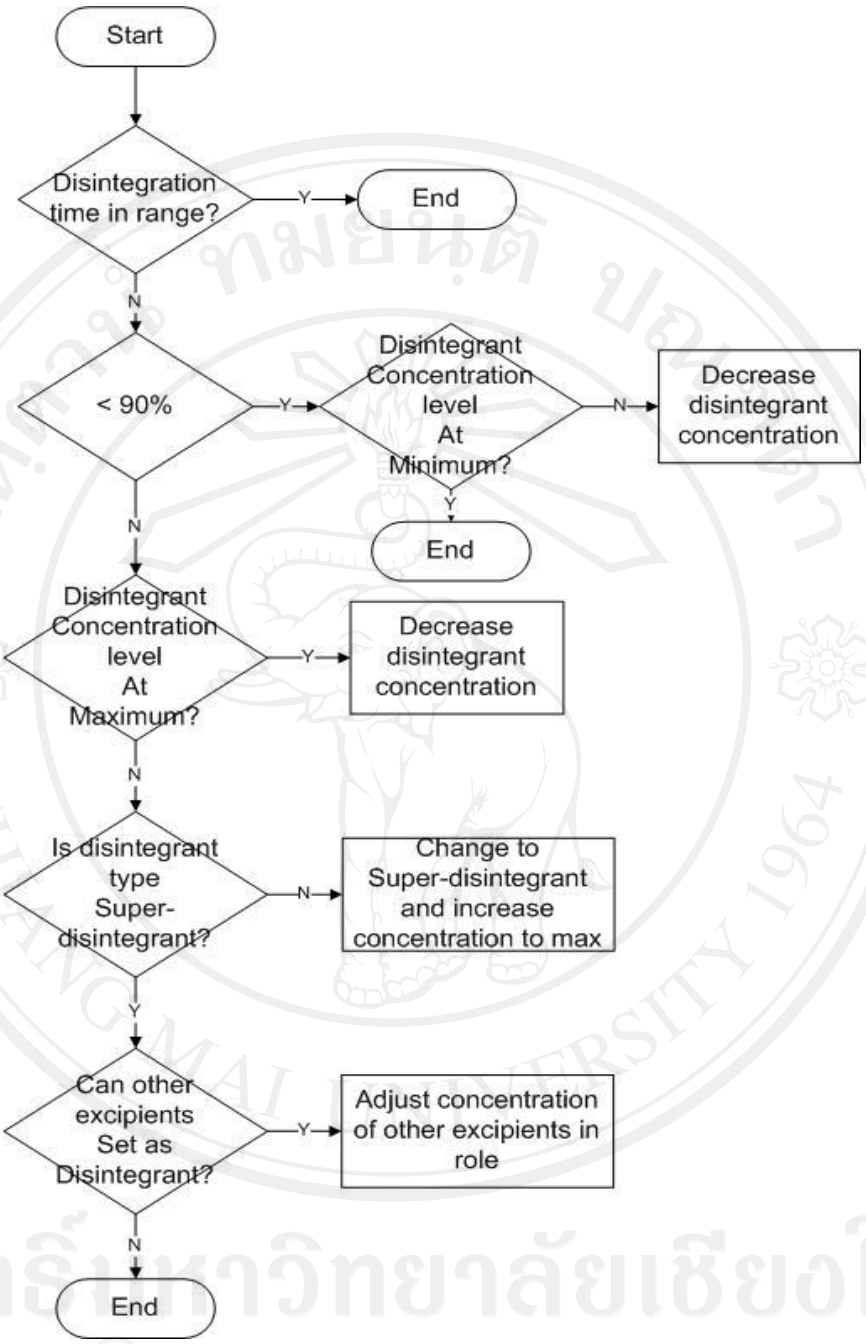

Figure 3.5 Flowchart of improving disintegration time

The second issue is a difference between dissolution profiles. The focused is the point average value of 5 minute point and 10 minute point in dissolution profiles since the two points are an initial raising point. Moreover, they basically are an explicit point that leads to unacceptable dissolution profile of API. Equation (3) is

applied to calculate the focus point. If the difference score at the focused point in dissolution profile is out of range (10%), solubilizer is focused rationally. Figure 3.6 shows steps to improve dissolution profile issue. To prevent an repetitive suggestion in this decision flow, the already executed part is not allow to execute again and it is ignored even the condition is fulfilled.

$$Focus\ point = \frac{[Original\ at\ 10]-[Original\ at\ 5]}{2} - \frac{[Generic\ at\ 10]-[Generic\ at\ 5]}{2} \quad (1)$$

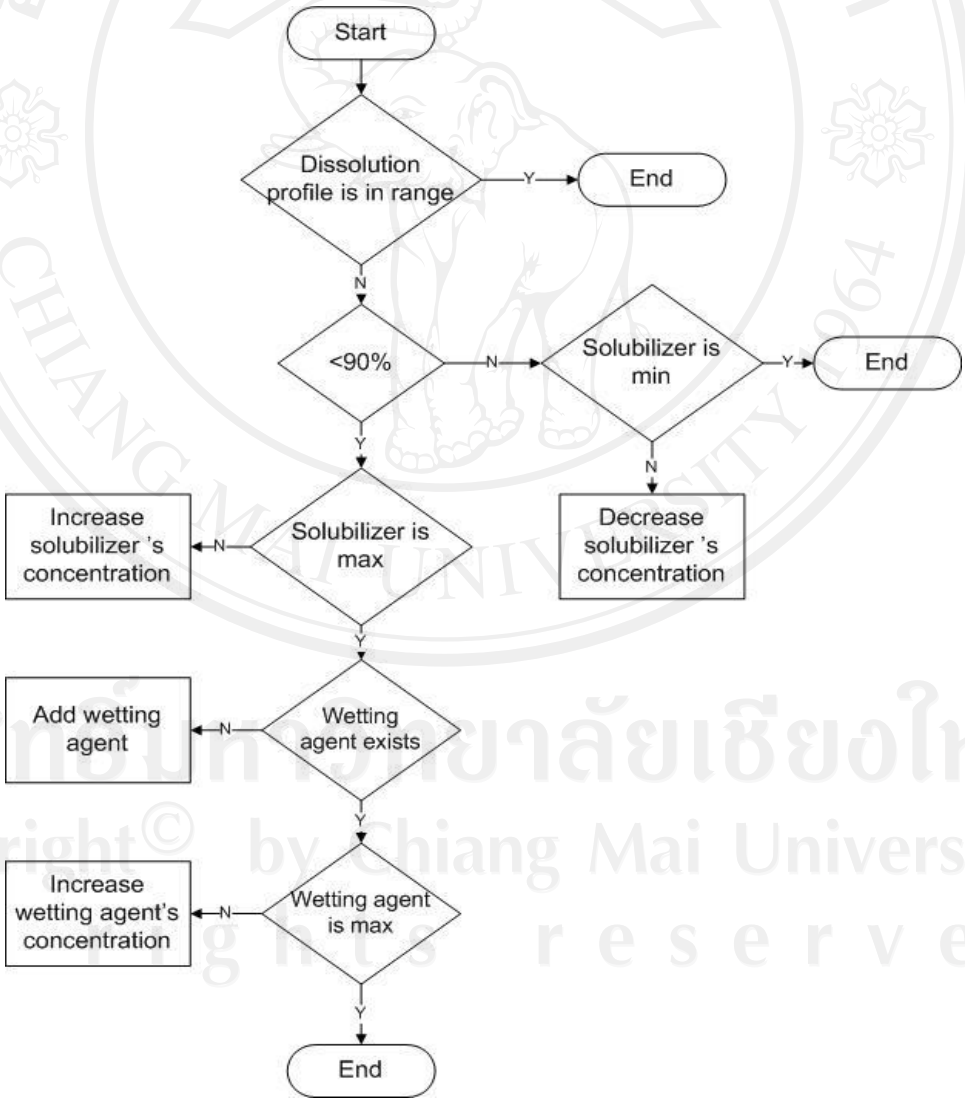

Figure 3.6 Flowchart of improving dissolution profile

3.3 OXPIRT System

3.3.1 OXPIRT architecture

OXPIRT system uses knowledge represented in ontology and a set of production rules as its main information. In this system, the information is used to infer a result by using an inference engine. Jess inference engine is exploited as an intellectual brain of the system to infer a result based on such little information as a fact.

Jess (Friedman-Hill, 2003) is one inference engine tool among other. Jess is a rule engine and scripting environment written entirely in Sun's Java language by Ernest Friedman-Hill at Sandia National Laboratories in Livermore, CA, USA. Jess is small in size and the fastest rule engines available. Its powerful scripting language gives an accessibility to all of Java's APIs.

Jess uses an enhanced version of the Rete algorithm to process rules. Rete is a very efficient mechanism for solving the difficult many-to-many matching problem. Jess has many unique features including backwards chaining and working memory queries. For more information, Jess can directly manipulate and reason about Java objects. Jess also allows to create Java objects and to implement Java interfaces without compiling any Java code.

However, ontology and instances in that representation cannot be directly used with Jess. They are stored in OWL format, extension of XML with additional marked up style of schema. It is needed to be transformed into JessML, which is Jess readable and recommended format, by applying XSLT processor(Groppe and Groppe, 2008).

With data formatting in JessML, all ontology information and instances are ready to be used in Jess inference engine effectively.

An overview of the system is illustrated in Figure 3.4. It consists of four modules.

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

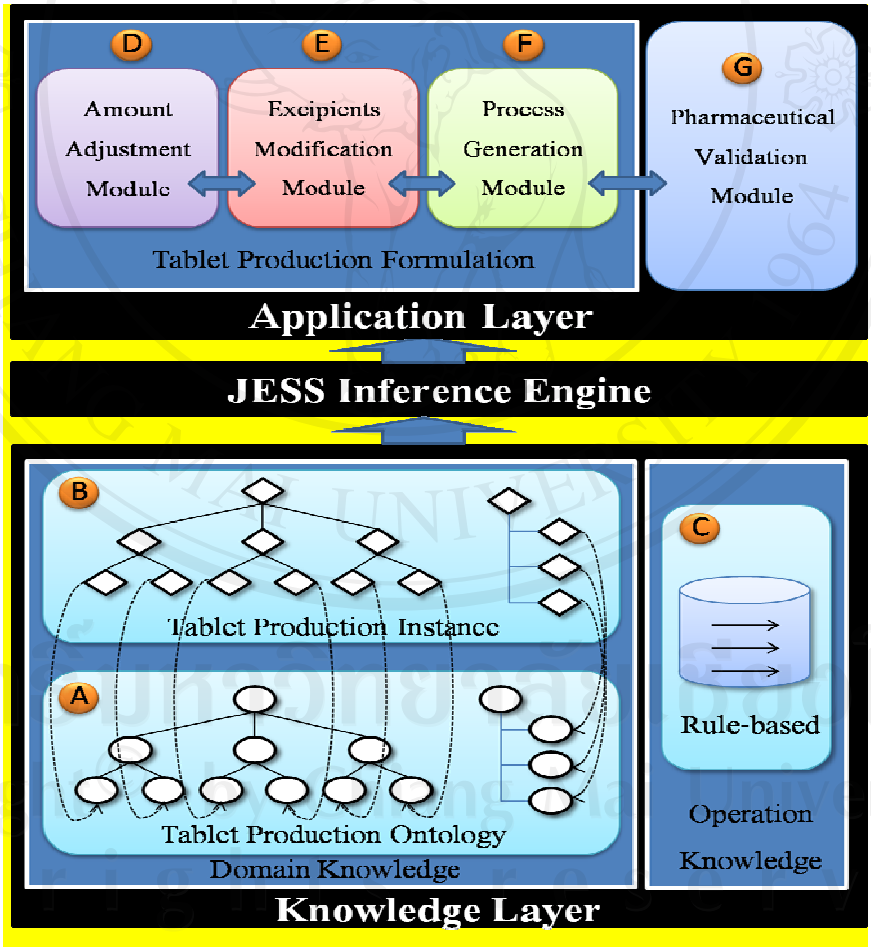

Figure 3.7 A framework of OXPIRT system

3.3.1.1 Amount adjustment module

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

3.3.1.2 Excipients modification module

Normally, a patent give us information of main drug and all excipients. In the formulation provided from the system, we will not modify excipients but only design amount of them. Since there are varieties types on each excipient, it is possible to apply different type when compare to the information from a patent. The objective of this module is to modify excipients if the given ingredients cannot formulate the appropriate tablet production of generic drug because of a limitation of excipient amount range and instrument. Excipients modifying is a strategy to be applied with amount adjustment module, and propose a new generic drug formulation. Modifying strategy is either adding or substitution which is chosen depending on a role of the focusing excipient. Whenever the new ingredients are determined, amounts of all excipients have to re-calculate in amount adjustment module.

3.3.1.3 Process generation module

This module is subjected 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.

3.3.1.4 Pharmaceutical validation module

This module is designed to evaluate the pharmaceutical equivalence between the standard quality of original product 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 (Shargel and Kanfer, 2005). The difference factor (f_1) is a measurement of the relative error between the generic drug formulation curve and the original product formulation curve whereas the similarity factor (f_2) is the measurement of dissolution curve between the generic drug and the original product. If the f_1 values range between 0 and 15 and f_2 values range between 50 and 100, both dissolution curves are equal. 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 go beyond the acceptable range. These factors can be determined using the following equations:

$$f_1 = \left\{ \frac{\left[\sum |R_t - T_t|\right]}{\left[\sum R_t\right]} 100 \right\} \quad (2)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{I}{n} \sum w_t \left(R_t - T_t\right)^2 \right]^{-0.5} 100 \right\} \quad (3)$$

Where: *f* is a fit factor; R_t is a reference assay at time t (percent dissolved); T_t is a test assay at time t (percent dissolved); n is a number of sample points; w_t is a weight at time t and it is constantly set to 1 in this study; ∑ is a summation of t from 1 to n. Note that f1 reflects the cumulative difference between the two curves at all time points, and is a measure of relative error between the two curves. Conceptually, f_1 which is a function of the average absolute difference between the two dissolution curves could be referred as a 'difference' factor. On the other hand, f_2 metric is a function of the reciprocal of mean square-root transform of the sum of square distances at all points. Conceptually, f_2 which is a measure of the similarity in the percent dissolution between two curves could be referred as a 'similarity' factor. When the two profiles are identical, f_2 = 50*log(100) = 100, and when the dissolution of one production is complete before the other begins, $f_2 = 50log\left\{\left[1 + (1/P)\sum_{i=1}^{P}|10|^2\right]^{-1/2} * 100\right\}$ = -0.001which can be rounded to 0. Thus the value of f_2 ranges between 0 to 100 with a higher f_2 value indicating more similarity between the two profiles.

In a real life situation, due to the original-generic variation in dissolution profiles, it is not expected to have f2 value be anywhere near 100 even when the two dissolution curves are generated from the same production of tablets. A generic product is therefore accepted as 'similar' to an original product if the dissolution profile difference between the two products is no more than the dissolution profile difference between the two products. Empirically, the experience in dissolution data analysis leads one to believe that an average difference of no more than 10% at any

sample time point, of the products of the same formulation may be acceptable. When this 10% average difference is substituted in the equation 3, f_2 becomes:

$$f_2 = 50log\left\{\left[1 + (1/P)\sum_{i=1}^{P}|10|^2\right]^{-1/2} * 100\right\}$$

$$= 50log\{\lceil 101\rceil^{-1/2} * 100\}$$

$$= 50*\log(9.95037) = 49.89$$

which may be rounded to 50 for simplicity. Dissolution of a generic product is therefore considered to similar to that of the original product if the f2 value of the two true profiles is not less than 50. It is clear that once the average distance at any sample time point between any two products is defined, the similarity limit based on f2 can be defined independent to the generic product or the original product and independent to the number of sampling time points to be used in the assessment of dissolution similarity(Shah et al., 1998).

3.3.2 Work Flow of OXPIRT

Since this work principally focuses on generic drug tablet production, a work flow for generic drug tablet development is mainly described. In this system, a work flow process can be separated into four processes; 1) preformulation process; 2) generic drug tablet formulation process; 3) laboratorial experiment process and 4) pharmaceutical equivalence validation process. The first and the third process are processes that user has to gather the necessary information for system. The second process is a process to generate a suggestion of generic drug formulation. The last process is for automatically validating a result of the second process. It determines

whether the result is acceptable or not. Unless it is acceptable, the system will pass to regenerate another formulation in the second process.

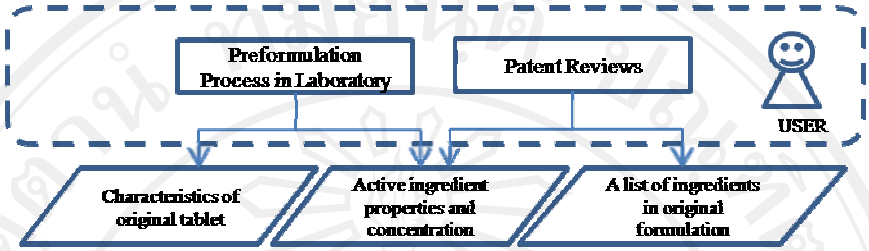

Figure 3.8 A preformulation process by user

Preformulation process is a process for user to gather information from both experiment of an original product in laboratory and a patent reviewing. From a preformulation process in laboratory, user acquires characteristics of original product tablet and main drug properties such as flowability and compressibility. From original product patent reviewing, user gains a list of excipients, the main drug with its amount, and its properties such as solubility and stability. Information from both processes is executed for the generic drug tablet formulation process. Figure 3.8 shows work flow of preformulation process. The rest processes are illustrated in Figure 3.9.

3.3.2.1 Generic drug tablet formulation

Generic drug tablet formulation is a process to generate a generic formulation based on the input from preformulation process. In this process, the system returns a generic drug production which includes all ingredients with their amount and a set of instructions.

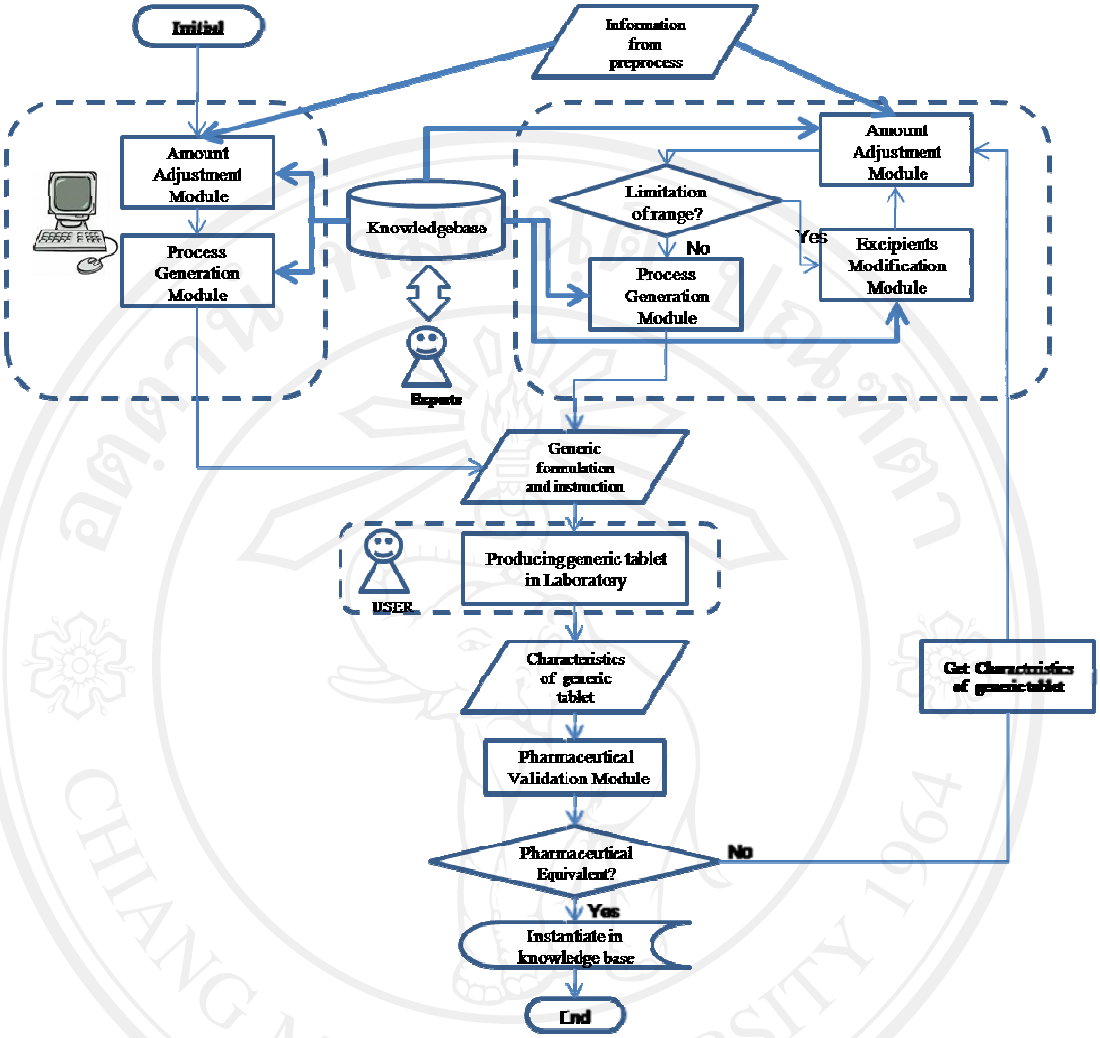

Figure 3.9 A work flow of the system

With only information of original product, the system initially sets up amount values of excipients at amount adjustment module. An example of interface for filling information of original product tablet is illustrated in Figure 3.10.

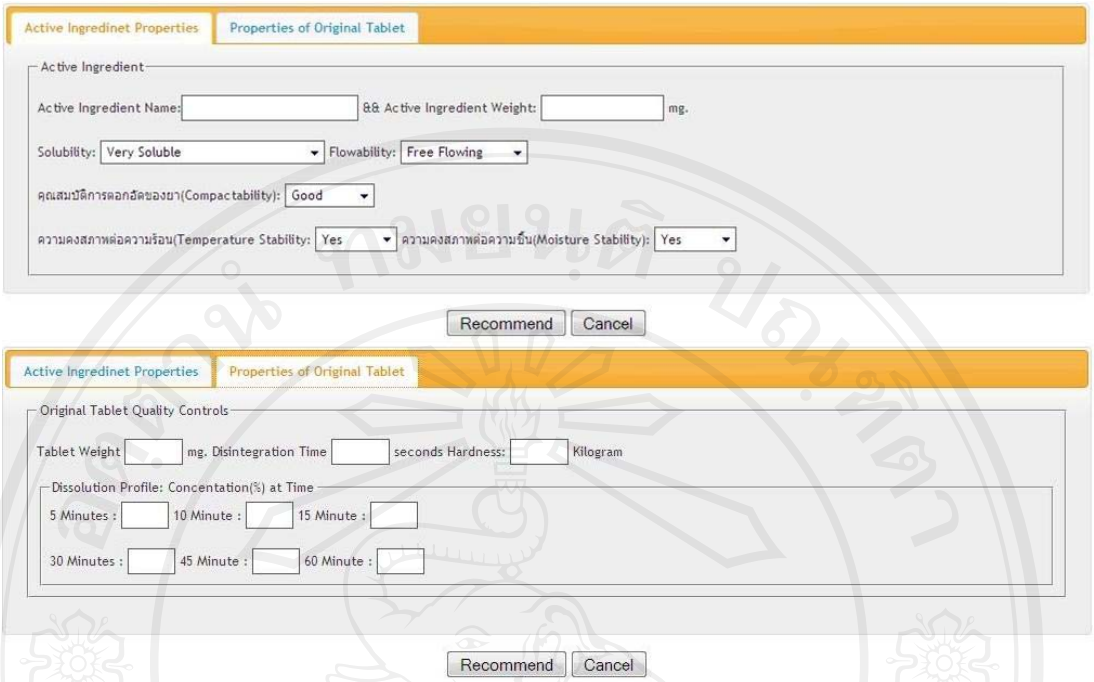

Figure 3.10 A user interface for getting the characteristics of original product tablet

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. The formulation result is consequently transferred to process generation module to generate a set of instructions based on those values. An example of output which includes a list of ingredients with generated amount values and a set of instructions is shown in Fig 3.10.

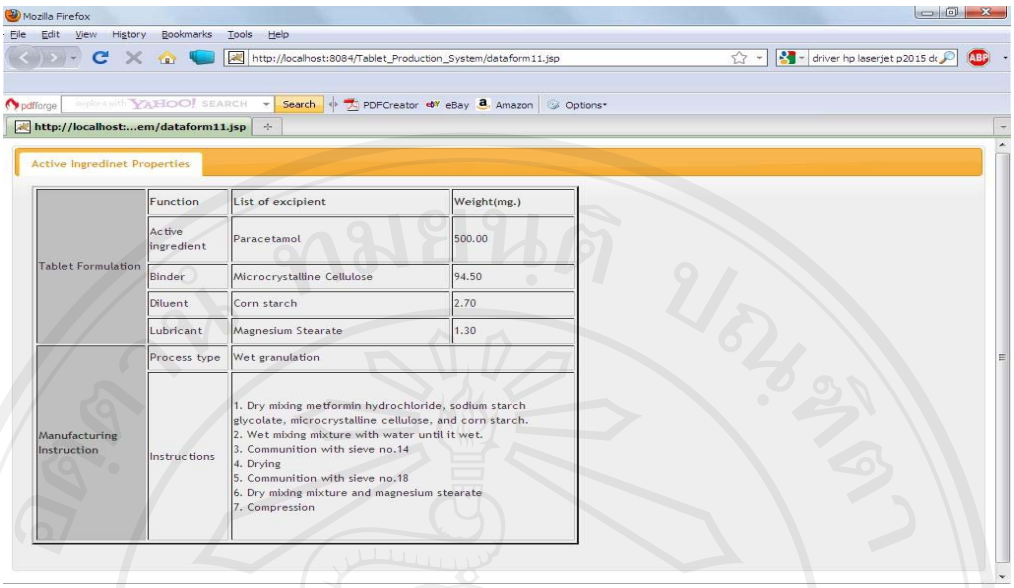

Figure 3.11 An output of tablet production

After the system returns a result, a generic drug tablet will be apparently produced according to output and the produced tablet will be tested for quality controls in laboratory. This testing informs details of the produced tablet such as dissolution profile, integration time, and hardness. There might be few chances that the first attempt can generate an unacceptable result.

In case of unacceptable result, the details from quality control can be utilized as additional information. The more information is entered to the system, the more specific amount of ingredient can better be adjusted reliably. However, there are very few cases that the amount value of excipients cannot be adjusted in the limitation range because of the implicit information from patent. The implicit information can be exemplified as a different particle size of excipient, and a variety of a crystal form of excipient therefore the excipient modification module is designed for handling these issues. With the details from quality control apart from original product information, the system has sufficient information to modify excipients.

In the excipient modification module, excipient can be grouped into two types, an excipient involving dissolution and an excipient effecting disintegration time. The modification is evoked differently according to the excipient type. For an excipient involving dissolution type, adding is evoked firstly. Otherwise, substituting strategy is primary alternative for an excipient effecting disintegration time type. Until there is no other alternative for primary strategy, another strategy will be chosen. When the result in formulation is created, the process must return to amount adjustment module to adjust an amount value.

The system works iteratively until the result is acceptable and is validated in generic drug validation process. Figure 3.11 shows a snapshot of the suggested generic tablet production. It is illustrated in suggestion list with amount of ingredients, and process for producing a generic drug tablet.

3.3.2.2 Generic Drug Validation

In this validating system, an input is the test result of quality controls which is important part to approve characteristics of original product. The equations to calculate the pharmaceutical equivalence are described in section 3.3.1.4. Figure 3.12 shows a snapshot of the interface for entering generic drug tablet characteristics. For those generic drugs whose their characteristics are pharmaceutically equivalent, the system displays a message to notify the user as illustrated in Figure 3.13. The equivalent generic drugs are stored in instance database and later are updated in the domain knowledge. However, the generic drugs whose their characteristics are not satisfactory will be sent back to Generic Drug Tablet formulation to generate another alternative.

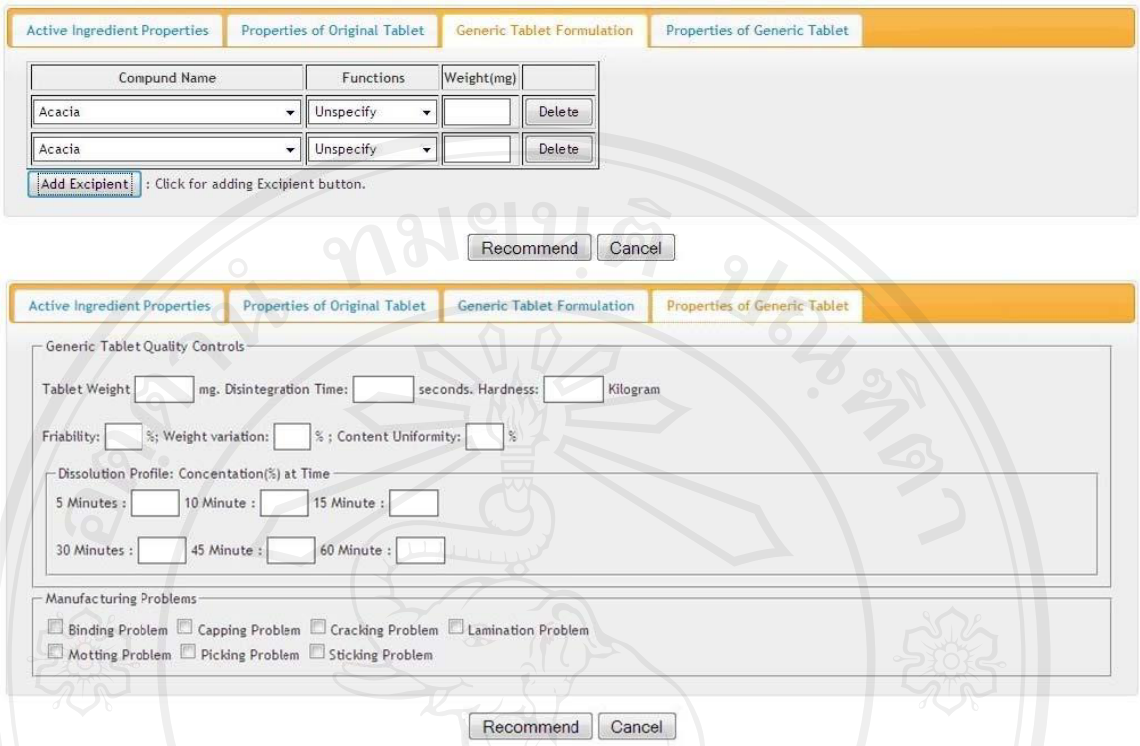

Figure 3.12 A user interface for getting testing result of the suggested generic drug tablet

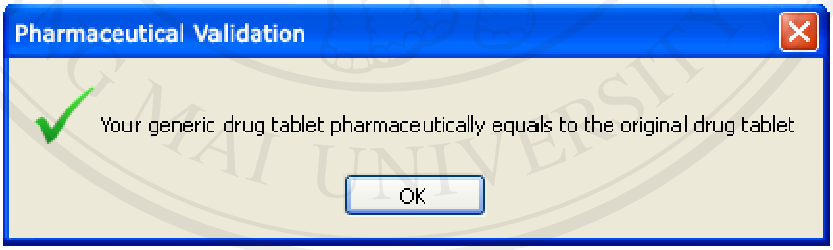

Figure 3.13 A notification of pharmaceutical equivalence

For applying OXPIRT to herbal tablet production, the workflow still goes the same way as a generic drug tablet production but unnecessary processes that relate to original product information extraction and pharmaceutical equivalence will not be executed. The unnecessary processes include patent reviewing, characteristics of original product study, and pharmaceutical equivalence validation. In different point of view, physicochemical properties of herbal drug are focused instead since herbal

product only requires passing a standard of tablet quality control, not original equivalence.

3.3.2.3 Herbal tablet formulation

For herbal tablet formulation, user interface and flow are mostly the same to a generic drug formulation. Unlike generic drug formulation, herbal tablet does not have its original to compare with. Therefore some parts of the given flow in Section 3.3.2.1 relevant to original product are excluded. In fact, a formulation of herbal tablet can have several possible alternatives which can pass standards of quality control. The result formulation and production from OXPIRT; therefore, might not be the best option for the herbal tablet.

To assign excipient roles for herbal tablet formulation, characteristics of herbal API are a certain clue. The influent characteristics include flowability, compactability, moisture stability and temperature stability. The information can be obtained by herbal API preformulation.

Like the generic one, the system initializes with allocating a manufacturing process based on two factors; flowability and compactability. Actually, herbal powder potentially has poor flowability and poor compactability. Thus, wet granulation is the proper process and becomes a default process for herbal tablet production.

For setting necessary functions for formulating tablet, the preformulation information is focused. For example, poor flowability herbal API constantly needs binder in formulation. With a set of necessary functions, an excipient is selected and assigned amount or concentration based on it. To find a proper excipient suitable to

the function and compatibility, all preformulation information is definitely concerned in great in detail.

After OXPIRT suggests a production of herbal tablet, it is brought to produce in laboratory scale and examine in term of quality control without pharmaceutical equivalence requirement. Hence, validation method in Section 3.3.2.2 is not necessary for herbal tablet production.

3.4 OXPIRT evaluation method

To test an ability and accuracy of OXPIRT, tablets produced regarding to a result of OXPIRT are evaluated. There are two groups of tablet productions that are focused: 1. Generic drug tablet production and 2. Herbal tablet production.

3.4.1 Evaluation of generic drug tablet production

In generic drug tablet production testing, drugs are separated into groups by two factors which relate to active ingredient (API) information. The first factor is a solubility of active ingredient which split into two types: A1) better than soluble API and A2) worse than sparingly soluble API. This factor indicates that the worse solubility the API contains, the more challenging on the formulation will become. The challenging involves the selecting of excipient that improves API's dissolution and overall performance. Otherwise, the better soluble generally cause less problem in excipient selecting and amount adjusting.

The second factor is a percentage amount of API per manufactured tablet which is focused only two types based on a criterion of content uniformity: B1) API less than 25% and B2) API more than 25%. The amount of API less than 25% per

tablet signifies the difficulty on blending to homogeneous mixture since a large amount of each excipient is combined together. For API more than 25% of total tablet weight, it is hard to find an appropriate amount of excipients since the space for amount adjustment is too narrow.

Combination of these two factors can generate four different groups of drugs. A representative from each group selected, which is four in total, is shown in Table 3.4.

Table 3.4 The four testing representatives from two factors

		Dose and ratio of API	
		B1) API >25%	B2) API<25%
Solubility of API	A1) Very soluble, Freely soluble, or Soluble	Metformin Hydrochloride	Hydroxyzine Hydrochloride
	A2) Sparing soluble, Slightly soluble, Very slightly soluble, or Practically insoluble	Paracetamol	Atorvastatin Calcium

3.4.1.1 Materials

Chemical

- Atorvastatin Calcium (Apotex Pharmachem Inc., USA)
- Hydroxyzine Hydrochloride (Shpngxin, China)
- Metformin Hydrochloride (Abhilash, India)
- Paracetamol (O.V. Chemical, Thailand)
- Calcium carbonate (Aldrich Chemical Company Inc., USA)
- Croscarmellose Sodium (FMC Biopolymer, USA)
- Sodium Starch Glycolate (Blanver, Brazil)
- Microcrystalline Cellulose (Fluka Chemika, Switzerland)

- Sodium Lauryl Sulphate (O.V Chemical, Thailand)
- Tween 80 (O.V Chemical, Thailand)
- Magnesium Stearate (Riedel-de Haën, Germany)
- Colloidal Silicon Dioxide (O.V Chemical, Thailand)
- Povidone K30 (BDH Prolabo, France)
- Corn Starch (O.V Chemical, Thailand)
- Lactose (O.V Chemical, Thailand)

Equipment

- Tablet Hardness Tester Monsanto (Type GPIT 9544)
- Hot air oven (Mermert type UM-500, Germany)
- Disintegration Tester (Pharma Test, Type PT21, Germany)
- Dissolution Apparatus (Hanson Research, Sr2 Dissolution test station. Hanson Research corporation, USA)
- UV-visible Spectrophotometer (Milton Roy Spectronic 1001 plus, USA)
- Hydraulic tableting machine (Carver Laboratory, Press Model C, USA)
- Sieve No. 10, 14, 20 (USA Standard Sieve Testing)
- Balance (Sartorius GMBH, Type 1702, Germany)

3.4.1.2 Method for evaluating generic drug tablet production

For testing methodology, there are five steps as follows:

a. Filling in the mandatory information of original tablet which is

i. Active ingredient name

ii. Active ingredient weight

iii. Tablet weight

iv. Hardness

v. Disintegration time

vi. Dissolution profile

vii. Flowability and

viii. Compactability

b. Running the system and receiving output to produce a tablet in a laboratory scale.

c. Testing the produced tablet in terms of

i. Hardness

ii. Disintegration time and

iii. Dissolution profile based on drug protocol.

d. Comparing dissolution profiles between the produced tablet and original information using equation mentioned in Section 3.3.

e. End if the result is pharmaceutical equivalence. If not, filling in the result from step (c) and repeat step (a) to (d).

3.4.2 Evaluation of Herbal tablet production

In Herbal tablet production testing, two samples are selected: 1). Ginger powder and 2). Fa-tha-lai-chon powder

3.4.2.1 Materials

Chemical

- Ginger powder
- Fa-tha-lai-chon powder

- Povidone K90 (Serva Feinbiochemical GmbK&Co., Germany)
- Povidone K30 (BDH Prolabo, Franch)
- Talcum (O.V. Chemical, Thaland)
- Magnesium Stearate (Riedel-de Haën, Germany)
- Isopropyl Alcohol (O.V. Chemical, Thailand)
- Microcrystalline Cellulose PH101(Fluka Chemika, Switzerland)

Equipment

- Tablet Hardness Tester (Monsanto Type GPIT 9544)
- Hot air oven (Mermert type UM-500, Germany)
- Disintegration Tester (Pharma Test, Type PT21, Germany)
- Friability Tester (Pharma Test, Type PTF 20F, Germany)
- Single Punch tableting machine (Hanseaten Type EI, Germany)
- Sieve No. 10, 14, 20 (USA Standard Sieve Testing)
- Balance (Sartorius GMBH, Type 1702, Germany)

3.4.2.2 Method for evaluating herbal drug tablet production

For testing methodology, there are five steps as follows:

a. Filling in the mandatory information of herbal powder which is
   i. Herbal name
   ii. Herbal weight
   iii. Flowability and
   iv. Compactability.

b. Running the system and receiving output to produce a tablet in a laboratory scale.

c. Testing the produced tablet in terms of

   i. Disintegration time

   ii. Weight variation and

   iii. Friability.

d. End if the result passes the standard of disintegration time, weight variation, and friability. If not, filling in the result from step (c) and repeat step (a) to (d).