CHAPTER 2

LITERATURE REVIEW

2.1 Tablet development and production

A tablet is one of dosage form of drug among other dosage forms which are capsule, syrup, inhaler, liquid injection, pure powder and solid crystal. The compressed tablet is the most widely used dosage form because it gives advantages for all concerned in both production and consumption of medical product.

Tablets are solid preparations each of which contains a single dose of one or more active ingredients. They are all obtains by compressing uniform volumes of particles. Moreover, tablet is a dry dosage form which promotes for their stability and long lives measured in years. They are also convenient for carrying and transportation because of their small size and strong solidity. Actually, almost of tablets are intended to be swallowed intact. To prevent unpleasant taste, modern tablets are coated for easier consumption.

In tablet development, tablet formulation is needed to be designed. Tablet dosage forms have to satisfy a unique design compromise. In fact, the ingredients using in tablet formulations are generally composed with two major parts; active pharmaceutical ingredients (API) and excipients. An active ingredient is the substance in a pharmaceutical drug or a pesticide that is biologically active. Alongside, an excipient is the additives used to convert pharmacologically active ingredients into pharmaceutical dosage forms suitable for administration to patients (Wade and

Weller, 1994). In very rare cases, some active ingredients may be tableted as pure substances, but most modern formulations include excipients.

In formulation design, the desired properties of rapid disintegration and dissolution of the active ingredients must be balanced with the manufacturability and esthetics of a solid compact resistant to mechanical attrition (Augsburger and Zellhofer, 2007). Excipients are critical to the design of the delivery system and play a major role for determining its quality and performance (Chowhan, 1993). Many possible excipients are available for designing a formulation, but several certain factors, for instance physical stability, chemical stability, and physiological inertness, restrain them to be selected. The major issue on design a tablet formulation is excipient that is incompatible with the active ingredient or with other excipients. Hence, a tablet formulation is not a random combination of ingredients, but rather a very carefully rational formulation designed to satisfy above criteria. Table 2.1 shows a summary of types and functions of tableting excipients.

Whether working in a large established laboratory or a small research organization, formulation developers are well advised to take an overall look at the development process to assess the most rational approach to their particular needs and resources. The plan should focus on the assessment the possible influence of formulation and processing variables on bioavailability and manufacture. The flow chart of research protocol is illustrated in Figure 2.1.

Table 2.1 Summary of types and functions of tableting excipients (Chan and Chew, 2007)

Excipient	Functions	Examples
Diluent	To act as a bulking agent or filling material	Sugars, lactose, mannitol, sucrose Inorganic salts, primarily calcium salts Polysaccharides, primarily microcrystalline celluloses
Binders and Adhesives	To hold powders together to from granules for tableting	Sugars, glucose, syrup Polymers, natural gums, starch, gelatin or synthetic celluloses, polyvinylpyrrol- pyrrolidone (PVP), poly-methycrylate (Eudragit™)
Glidants	To improve the flow of granules from the hopper to the die cavity to ensure uniform fill for each tablet	Fine silica, magnesium stearate, purified talc
Disintegrants	To facilitate the breakup of a tablet in the gastrointestinal tract	Starch and derivatives ,polyplasdone XL Microcrystalline cellulose Clays, algins, gums, surfactants
Lubricants	To reduce the friction between the granules and die wall during compression and ejection of the tableting process	Water-insoluble: metal stearates, stearic acid, talc Water-soluble: boric acid, sodium chloride,benzoate and acetate, sodium or magnesium lauryl sulfate Carbowax 4000 or 6000
Antiadherents	To minimize the problem of picking, i.e., portion of the tablet face pinked out and adhered to the punch face during tableting	Talc, cornstarch, metal stearates, sodium lauryl sulfate
Colorants	For identification purpose and visual marketing values	Natural pigments Synthetic dyes
Flavors and sweeteners	To improve the taste of chewable tablets	Natural, e.g., mannitol Artificial, e.g., aspartame

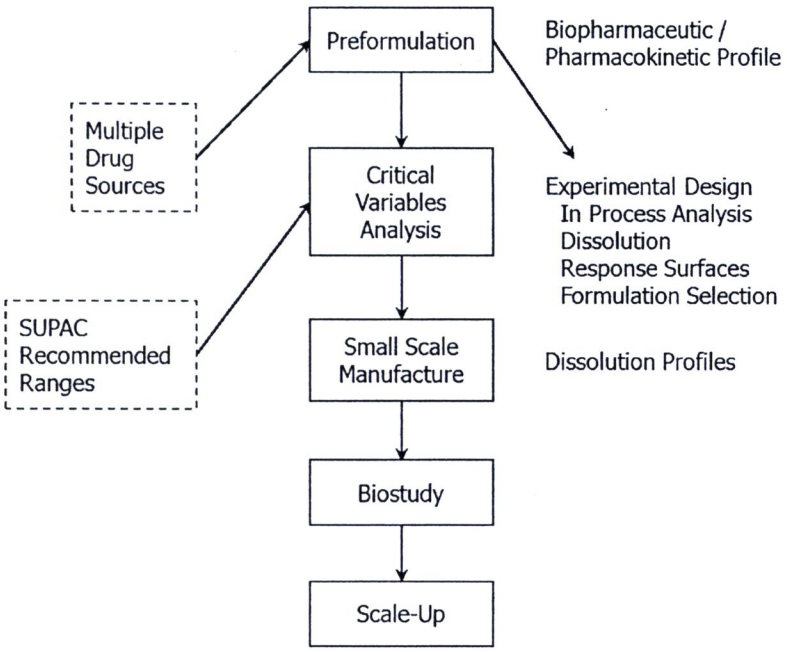

Figure 2.1 A flow chart of formulation development process

From formulation development, the first stage begins with a preformulation study. The objective of preformulation is to develop a portfolio of information about the drug substances to serve as a serve parameters against which detailed formulation design can be carried out (Armstrong, 2007). Preformulation investigations are designed to identify those physicochemical properties of drug substances and excipients that might influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product (Chan and Chew, 2007). Based on the preformulation information, decisions can be made regarding formulation design and process strategy. Initial guidance may be provided by the proposed dose.

In the critical variables analysis phase, a statistical experimental design is created intended to assess critical formulation and process variables. In these studies, the range of composition variables are chosen to at least encompass those

recommended in the AAPS-FDA Workshop on Scale-up of Immediate Release Oral Solid Dosage Forms or SUPAC (Armstrong, 2007).

Once a tablet formulation is designed, it is manufactured to produce a tablet. However, a tablet manufacture remains a complex process since a list of ingredients is only given with those properties which are necessary for the production of satisfactory qualified tablet. A well manufactured tablet should possess the following qualities:

1. It should, within permitted limits, contain the stated dose of drug.
2. It should be sufficiently strong to withstand the stresses of manufacture, transport, and handling.
3. It should deliver its dose of drug at the site and at the speed required.
4. Its size, taste, and appearance should not detract from its acceptability by patient.

2.1.1 Method of tablet manufacture

To produce a drug into tablet dosage form, three methods of tablet manufacture are available as follows: wet granulation, dry granulation and direct compression.

Wet granulation is the traditional method of pretreatment of solid prior to tableting. Despite its complexity and inherent disadvantages, about half of tablets produced worldwide are currently manufactured by this process. Its essence in the particles of active ingredient, with a diluent if necessary, are stuck together using an adhesive, the latter usually being water-based. The result is a granular product which flows more readily and has an improved ability to cohere during compression. A flow

diagram of the wet granulation process together with appropriate excipients is shown in Figure 2.2.

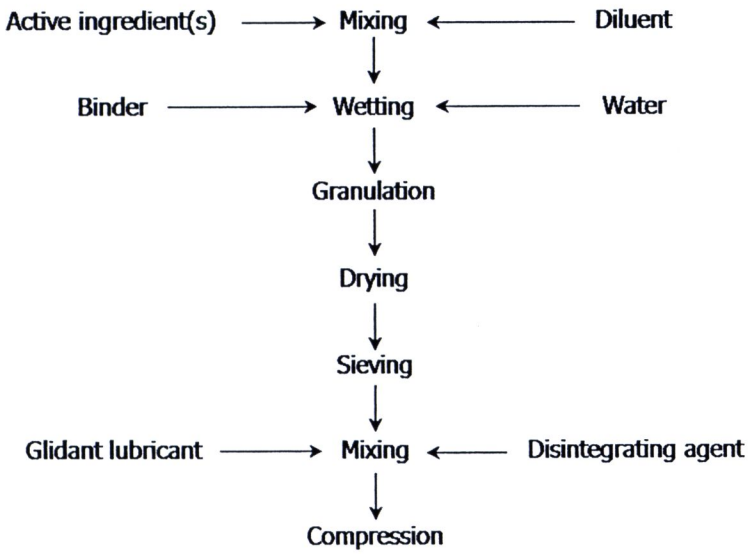

Figure 2.2 A wet granulation process

Dry granulation is an alternative method which can be used since wet granulation method of tablet manufacturing suffers from its several disadvantages. The components of the formulation are compressed in the dry state. Unless sufficient bonding strength is achieved by compression alone, a binder needs to be added in the dry state. An overview of dry granulation process is sketched in Figure 2.3.

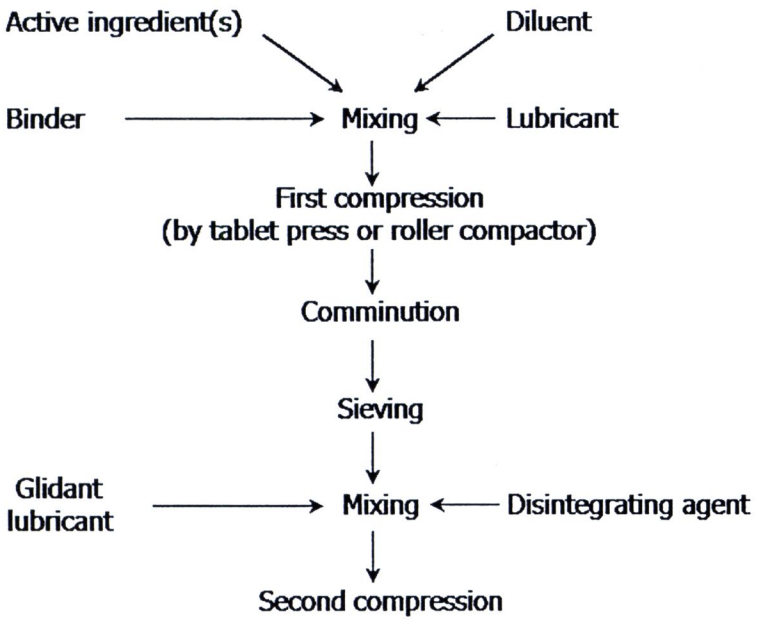

Figure 2.3 A dry granulation process

Both wet and dry granulation methods of tablet manufacture are complex multistage processes, but are necessary to convert the components of the formulation into a state that can be readily compressed onto acceptable tablets. Direct compression is another available method. This method is applied when granulation would be unnecessary because a major component of the formulation already possesses the necessary degree of fluidity and compressibility (Bolhuis and Chowhan, 1996). The key for direct compression is the diluent. This must not only possess those properties which are necessary for satisfactory tablet formulation, but also retain those properties when mixed with the other constituents of the formulation such as the active ingredient. In this process, the ingredients are mixed together and then compressed. Almost invariably a lubricant must be added, and a glidant and a disintegrating agent included when necessary. An obvious advantage of direct compression is that the

process does not involve the use of a liquid and a drying stage which reduces a cost on its attendant energy. The process of direct compression is visualized in Figure 2.4.

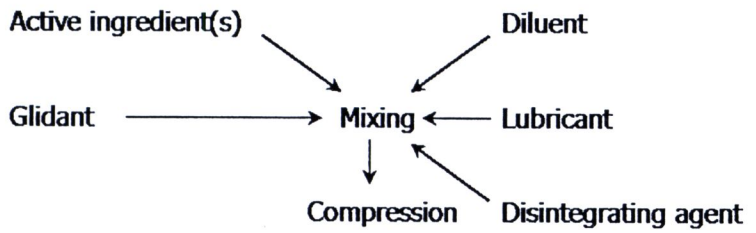

Figure 2.4 A direct compression process

2.1.2 Quality control of tablet

After a tablet is manufactured, it needs to be tested for quality control *in vivo* study phase. The quality control is an important phase to establish an *in vitro-in vivo* correlation (IVIVC). If an appropriate correlation can be established, dissolution may serve as a surrogate for vivo studies in the interpretation of what is significant and what is not among the variables studied (Augsburger and Zellhofer, 2007).

A quality control for tablets for official standards based on different pharmacopoeias is shown in Table 2.2. For non-compendial standards,

1. Measurement of mechanical properties is not covered in pharmacopoeial monograph. There are also a number of tests frequently applied to tablets for which there are no pharmacopoeial requirement but will form a part of a manufacturer's own product specification.

1.1 Hardness tests/ Crushing strength: The test measures crushing strength property defined as the compression force applied diametrically to a tablet which just fractures it. Among a large number of measuring devices, the most favored ones are Monsanto tester, Pfizer tester, and Strong cobb hardness

tester. All are manually used. So, strain rate depends on the operator. HeberleinSchleuniger, Erweka, Casburt hardness testers are motor driven.

1.2 Friability (Official in USP): The tablet may well be subjected to a tumbling motion. For example, coating, packaging, transport, which are not severe enough to break the tablet, but may abrade the small particle from tablet surface. To examine this, tablets are subjected to a uniform tumbling motion for specified time and weight loss is measured. Roche friabilator is most frequently used for this purpose.

2. Tests for coated tablets

2.1 Water vapor permeability

2.2 Film tensile strength

3. Coated tablet evaluations:

3.1 Adhesion test with tensile-strength tester: Measures force required to peel the film from the tablet surface.

3.2 Diametral crushing strength of coated tablet: Tablet hardness testers are used. This test gives information on the relative increase in crushing strength provided by the film and the contribution made by changes in the film composition

3.3 Temperature and humidity may cause film defects. Hence studies are to be carried out

3.4 Quantification of film surface roughness, hardness, and color uniformity. Visual inspection or instruments are used.

Resisilient films remain intact, and no color is transferred to the paper; very soft coating are readily erased from the tablet surface to the paper.

Table 2.2 A comparison of different pharmacopoeial quality control tests

Pharmacopoeias	Type of tablet	Tests to be performed
British Pharmacopoeia	For all tablet	Content of active ingredients Disintegration Uniformity of content Labeling
	Uncoated tablet	Disintegration test Uniformity of weight
	Effervescent tablet	Disintegration test Uniformity of weight
	Coated tablet	Disintegration test Uniformity of weight
	Gastro tablet	Disintegration
	Modified release tablet	Uniformity of weight
	Tablet for use in mouth	Uniformity of weight
	Soluble tablet	Disintegration test Uniformity of weight
	Dispersible tablet	Disintegration test Uniformity of dispersion Uniformity of weight
Indian Pharmacopoeia	Uncoated tablet	Uniformity of container content Content of active ingredient Uniformity of weight Uniformity of content Disintegration test
	Enteric coated tablet	Disintegration test
	Dispersible tablet	Uniformity of dispersion Disintegration
	Soluble tablet	Disintegration
	Effervescent tablet	Disintegration/dissolution/dispersion test
United State Pharmacopoeia	Physical tests applicable to tablet formulation	Bulk density /Tapped density of Powder Powder fineness Loss on drying Disintegration test Tablet friability Dissolution test Drug release testing Uniformity of dosage form Container permeation test Labeling of inactive ingredients

With an acceptable quality, a tablet is ready for mass production. Usually, a new developed drug is under patent protection. A patent is a grant of exclusive rights from government to inventors for their inventions in exchange for the inventors disclosing their inventions to society. Patent rights are limited in time and are also limited to the sole right of excluding other from making, copying, using and selling the inventions without permission.

2.2 A generic drug development

A new invented drug with patent protection is usually marketed at a price that recoups the cost of development over the remaining life of the patent or other exclusivity arrangement (Kibbe, 2007). Eventually, protection from competition is lost to other pharmaceutical companies or divisions of the companies that specialize in marketing expired patent drug (Suter and Giddings, 2007). They can apply to market the same active ingredients under its non-proprietary or generic name. The generic manufacturer is not required to do a complete clinical trial to prove effectiveness and safety because that has already been well established for the drug. However, it is importantly required to show that the generic drug product is equivalent to the original product. In Thailand, most drugs in market are a generic drug since it can be sold in lower price comparing to a brand name drug. There is a large economic incentive for the development of generic drug products, especially for highly successful drug products.

A generic drug production consists of two approaches. The former is the approach that has the same strategy as the original production, namely it initializes with preformulation and so on. The latter is a reverse engineering approach. This is a

top-down approach which begins by the step of decoding an original product for identifying a quantity of excipients. This shows information of excipients that mostly affects the formulation's performance (i.e., stability or dissolution profile). This step focuses on only important excipients (e.g., buffer, dissolution modifier and stabilizer) to find the best candidates for a reverse engineering. The second step is to analyze a solid-state characterization of active ingredient. This information gives safety to generic production for ensuring the same similar stability and dissolution profile to the original product. The last step is to identify the manufacturing process. The process can be predicted on the basis of the active ingredient's physicochemical profile. In addition to process ability, the manufacturing technique can affect the drug's stability and performance. Protocol for reverse engineering is sketched in Figure 2.5.

A generic drug is strongly required to have a pharmaceutical equivalence to the original product. To test a generic drug, manufacturers do not have to establish the clinical usefulness of the drug but only to ensure that the generic product with new formulation has the same relative in pharmaceutically equivalent to the innovator product.

Pharmaceutical equivalence is the condition in which generic drug products contain the identical quantity of an active ingredient (but not necessarily contain the same excipients) in an identical comparable dosage form. Moreover the generic drug must meet all applicable standards of identical strength, quality, purity and potency. The determination of pharmaceutical equivalence is considered with the following criteria:

- Identical amount of active ingredient(s)

- Same dosage form or comparable dosage form
- Same route of administration

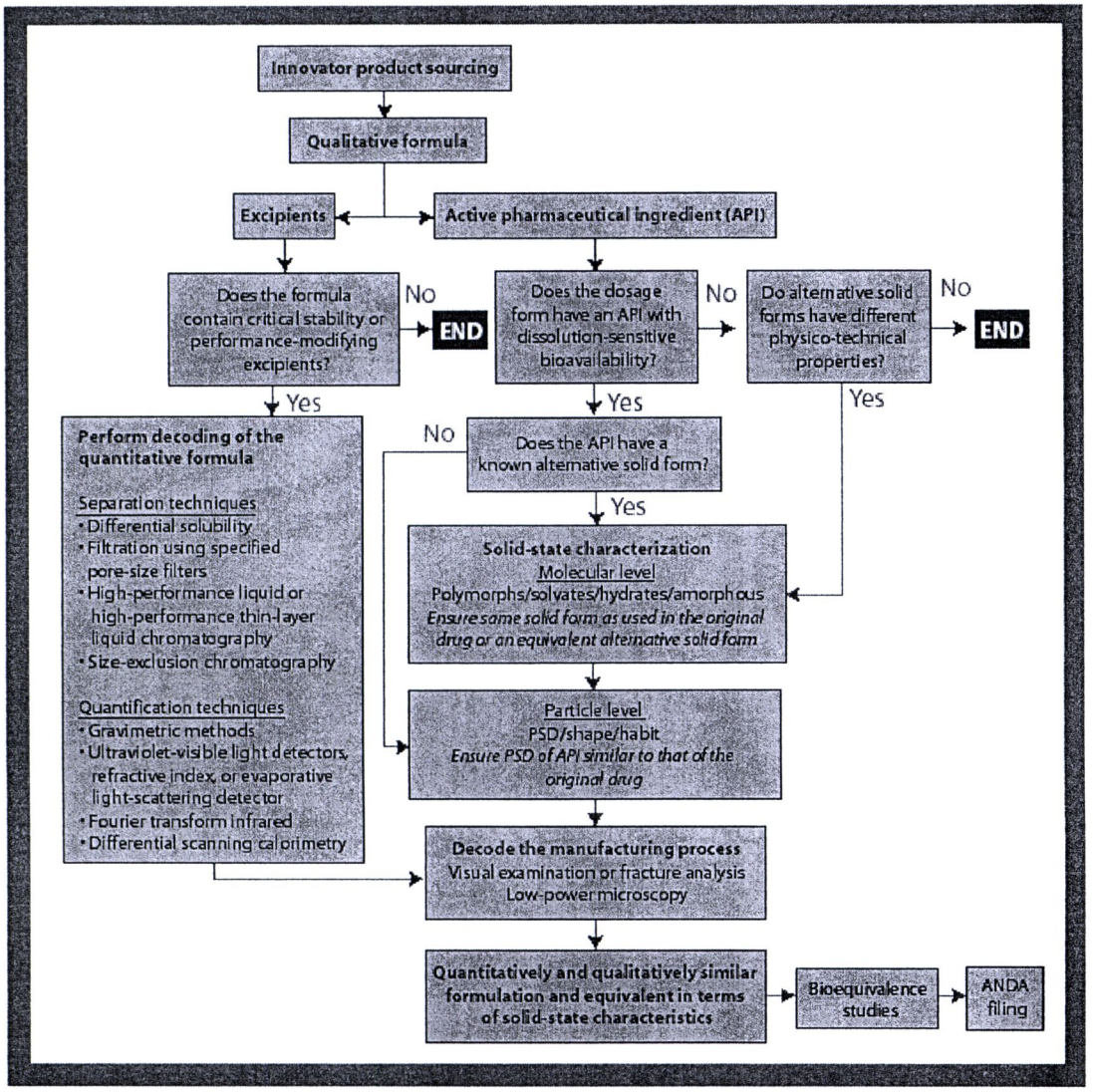

Figure 2.5 Protocol for reverse engineering (Bansal and Koradia, 2005)

It is noted that pharmaceutical equivalence does not necessarily apply to therapeutic equivalence. Therapeutic equivalence requires a product to be pharmaceutically equivalent and to have the same safety and efficacy profile after administration of the same dosage.

However, details given in patents are only provided with some parts of formulation including name of active ingredient with its quantity, list of used excipients without their quantity and a dosage form. It is not an easy task for reformulating by adjusting amounts of excipients. Considerable ingenuity and formulation expertise are greatly required in generic drug formulation to have certain pharmaceutical equivalence as same as the original product.

2.3 Herbal Tablet Production

An herbal tablet is defined as a tablet in which an herbal powder is modified to serve as an active ingredient. An herbal tablet is produced for transforming an herbal traditional drug into a dosage form for easier consumption, certain dose and comfortable mobility (Liberman and Lachman, 1980; Liberman and Lachman, 1981; Liberman and Lachman, 1982). To produce herbal tablet, three processes have to be executed. They are a preformulation study, a rational design and formulation, and a quality control (Department of medical sciences Ministry of public health, 1987; Jirawongse, 1995).

Like other drug preformulation, a preformulation study of a herbal tablet can be conducted by both a laboratory test and a document reviewing. It concerns about information of a characteristic of herbal ingredient including solubility, friability, compactability, compressibility, flowability, density and so on. However, it is hard to instantly estimate an appropriateness of a total dose and ration of a tablet in this initial process. Therefore, the total dose and ratio of the herbal tablet depends on the pharmacists who formulate the herbal tablet formulation.

A rational design and formulation process is a selection of excipients in a formulation and a selection of a manufacturing process. To properly select each excipient, information from preformulation is definitely taken into account. Generally, an herbal tablet production is designed with active ingredient, binder, disintegrant, diluent, and lubricant. For manufacturing process selection, a wet granulation is mostly chosen since most of herbal active ingredients are usually poor in both flowability and compactability.

A quality control for an herbal tablet is focused in weight variation, disintegration and friability of the produced tablets. For weight variation, the produced herbal tablets that the desired weight is over 325 mg. can have their weight varied for ±5%. For lower than 325 mg. per the produced tablet, weight variation is allowed for ±10%. To pass a disintegration standard, the produced herbal tablets are ensured to be completely disintegrated within 30 minutes from *in vitro* study. The friability of the produced herbal tablet is same as the standard of general tablet.

2.4 Ontology

Ontology is well known as conceptual knowledge representation using in several purposes. Ontology represents domain knowledge in the point of specific formal specification of the terms in the domain and relation among them (Gruber, 1993). The advantage of ontology has been widely canvassed and includes enabling the sharing of knowledge, the re-use of knowledge and the better engineering of knowledge based system with respect to acquisition, verification and maintenance (Jones et al., 1998).

In computer science and information science, an ontology is a formal representation of knowledge as a set of concepts within a domain, and the relationships between those concepts. It is used to reason about the entities within that domain, and may be used to describe the domain (Davies et al., 2006).

In theory, an ontology is a formal, explicit specification of a shared conceptualization. An ontology provides a shared vocabulary, which can be used to model a domain i.e., the type of objects and/or concepts that exist, and their properties and relations. For visualization, ontology definition is illustrated in Figure 2.6 (Lacy, 2004).

Ontologies are used in artificial intelligence, the Semantic Web, systems engineering, software engineering, biomedical informatics, library science, enterprise bookmarking, and information architecture as a form of knowledge representation about the world or some part of it.

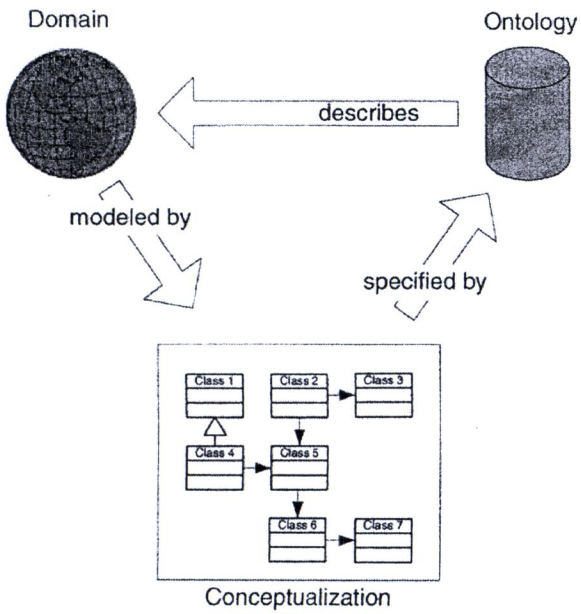

Figure 2.6 Ontology definition(Lacy, 2004)

Most ontologies are described by classes (concepts), relations, and individuals (instances). Class refers to a definition of concept in the same typology. In general ontologies, relation, which the definition is by word, is divided into two types; 1. hierarchical relation or class-subclass relation (hypernymy-hyponymy relation or is-a relation) and 2. part-whole relation (meronymy-holonymy relation or part-of relation). Individual indicates an instance or an object.

For example in Figure 2.7, the concept of bicycle is a super class of touring bicycles, utility bicycles, cruiser bicycles, mountain bicycles and racing bicycles. In the other word, touring bicycles, utility bicycles, cruiser bicycles, mountain bicycles and racing bicycles are all a sub class of a bicycle. In the deeper level, a mountain bike is a generalization of five sub-types which are a cross country bicycle, a trail bicycle, a down hill bicycle, a freeride bicycle and a dirt jump bicycle. For another deeper level, there are sprinter bicycle and endurance bicycle as a specification of a racing bicycle. This relation in ontology is identified as is-a relation to represent hierarchical organization among two or more concepts which are bicycles in this example.

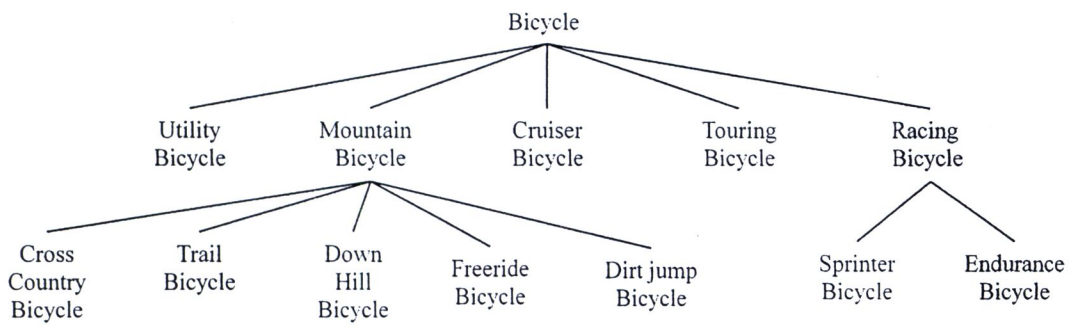

Figure 2.7 A Class hierarchy of bicycle concept

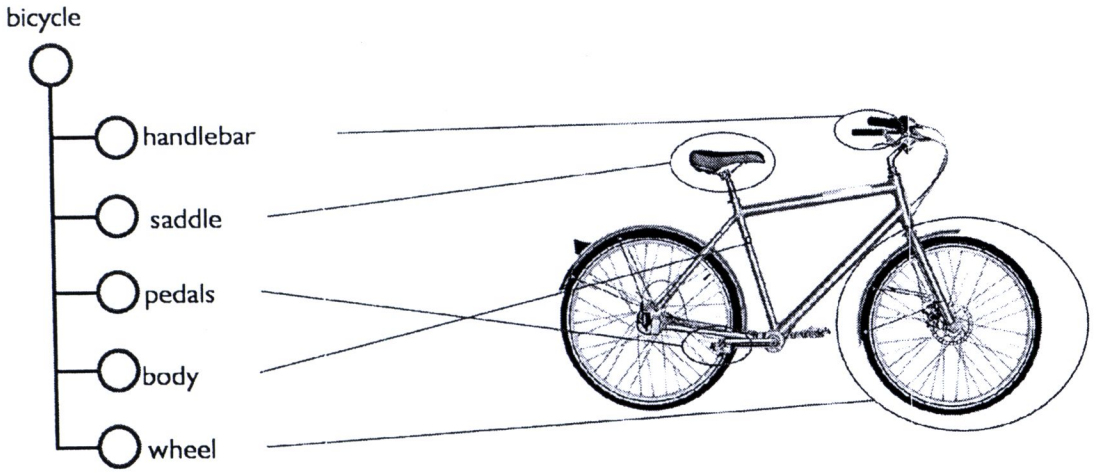

Figure 2.8 Part-whole relations of the bicycle concept

In Figure 2.8, part-whole relation of the concept bicycle is exemplified. The concept bicycle has a handle bar, a saddle, pedals, a body and wheels as the necessary parts. On the other hand, a handle bar, a saddle, pedals, a body and wheels are a part of a bicycle. The relation signifies a part-of relation between concepts of entities related to a bicycle. A part-of relation is an identification to show a part of a concept which requires least number of all parts to scope an available amount of a part. In ontology, an available amount is recognized as a term of cardinality.

An individual simply defines as an object, an attribute or an instance of a specific concept. Unlike aforementioned components, an individual refers to actual entities in the world, not concepts in an ontology.

For a summary, an ontology is usually developed for the purpose of categorization of concepts and their relations based on knowledge in a specific domain. Therefore, classes and relations of such an ontology generally are complex and hard to manage them efficiently since the language that enables all mentioned

complexity is web ontology language (OWL) which is complicated, certainly format-specific and hardly understandable for humans.

2.4.1 Web Ontology Language

The web ontology language (OWL) is a language for defining ontologies and associated individual data. Frame-based reasoning systems, Description logics, and existing web language influences OWL's development. The OWL was developed to represent computer-parseable information (Lacy, 2004).

The OWL is designed to make the language intuitive for humans and to have sufficient expressive power to describe machine-readable content needed to support Semantics Web applications. OWL satisfies the Semantics Web's requirement of providing minimal investment of human producers and consumers and supporting software requirements for a language with explicit semantics.

The resulting OWL language is based on the World Wide Web Consortium (W3C) standards and provides producers with information representation features to define their own ontologies and to extend others' ontologies. It supports expressive statement in a manner that supports scalability. OWL builds on the extensible markup language (XML) and allows users to provide machine-readable semantic annotations for specific communities of interest. OWL is used to make statements, called assertions, about classes, properties, and individuals. Assertions can be stated in a single ontology, or in a combination of multiple joined ontologies. In addition to explicit assertions, additional facts can be derived or logically entailed as a result of inferencing.

OWL builds on open W3C web standards and can be viewed as part of a Semantic Web's layered architecture with each increasingly powerful layer building on the layer below. Tim Berners-Lee defined an initial layered architecture view of the Semantics Web. Various alternative views of the layered architecture have since been developed.

Figure 2.9 presents a layered conceptual view of the Semantic Web. The layers shown are not layers in the sense of networking models but illustrate rough dependencies. Each layer depends on the layers beneath and uses their features to provide its capability. The figure shows that the top layer, the implementation layer, provides specific application. In the next layer down, the logical layer, OWL support formal semantics and reasoning. Below OWL, the Resource Description Framework (RDF) Schema (RDFS) language supports the ontological primitive layer (defines a vocabulary). RDF supports the basic relational language layer through its simple data model and syntax for making statements. RDF is serialized using RDF/XML. XML and XML Schema datatypes support the transport/syntax layer, and Uniform Resource Identifiers (URIs) and namespaces support the symbolic/reference layer.

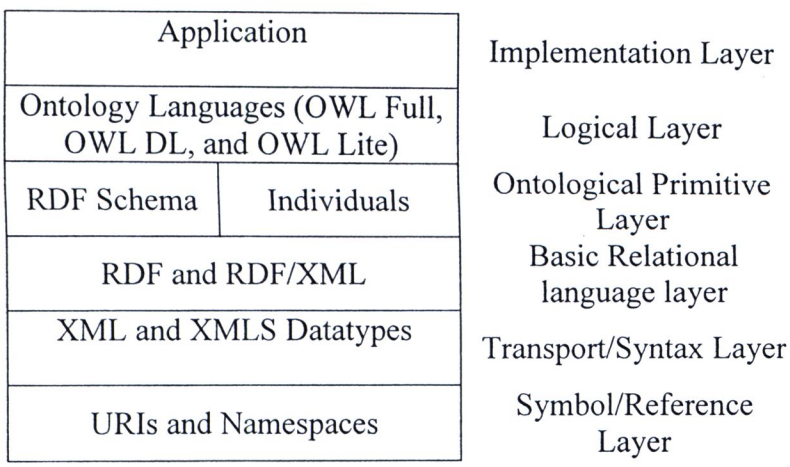

Figure 2.9 Semantic Web's Layered Architecture (Lacy, 2004)

With several benefits of the OWL, many ontologies are applied in this format. However, the OWL is a very format-specific and too complex for human to manually manage. For example, Figure 2.10 shows the OWL formatted data of some parts of the bicycle ontology mentioned in Figure 2.7 and Figure 2.8. The examples are very complicated and difficult to be manually crafted by humans.

2.4.2 Hozo Environment

Hozo environment(Kozaki et al., 2002) is a freeware tool for building ontologies based on fundamental ontological theories. Hozo includes an ontology editor and an instance editor. Its graphical interface is friendly provided for user to simply browse and modify ontologies by simple mouse operations. For computer-readable format, its ontology and resulting model are available in different formats (OWL, Lisp, Text, XML/DTD, DAML+OIL) which make them portable, reusable, and simply maintainable. A snapshot of the interface of the Hozo ontology editor is shown in Figure 2.11.

```
<owl:Class rdf:ID="bicycle">
    <rdfs:label>bicycle</rdfs:label>
    <rdfs:subClassOf rdf:resource="#Any" />
    <rdfs:subClassOf>
        <owl:Restriction>
            <owl:cardinality rdf:datatype="http://www.w3.org/2001/XMLSchema#nonNegativeInteger">1</owl:cardinality>
            <owl:onProperty rdf:resource="#has_bodypart" />
        </owl:Restriction>
    </rdfs:subClassOf>
    <rdfs:subClassOf>
        <owl:Restriction>
            <owl:onProperty rdf:resource="#has_bodypart" />
            <owl:allValuesFrom rdf:resource="#body" />
        </owl:Restriction>
    </rdfs:subClassOf>
    <rdfs:subClassOf>
        <owl:Restriction>
            <owl:cardinality rdf:datatype="http://www.w3.org/2001/XMLSchema#nonNegativeInteger">2</owl:cardinality>
            <owl:onProperty rdf:resource="#has_wheelpart" />
        </owl:Restriction>
    </rdfs:subClassOf>
    <rdfs:subClassOf>
        <owl:Restriction>
            <owl:onProperty rdf:resource="#has_wheelpart" />
            <owl:allValuesFrom rdf:resource="#wheel" />
        </owl:Restriction>
    </rdfs:subClassOf>
    <rdfs:subClassOf>
        <owl:Restriction>
            <owl:cardinality rdf:datatype="http://www.w3.org/2001/XMLSchema#nonNegativeInteger">1</owl:cardinality>
            <owl:onProperty rdf:resource="#has_handlebarpart" />
        </owl:Restriction>
    </rdfs:subClassOf>
    <rdfs:subClassOf>
        <owl:Restriction>
```

Figure 2.10 Some part of bicycle ontology in OWL format

In Hozo environment, all usual ontological components such as class, hierarchical relation, part-whole relation and individual are completely supported. Unlike other ontology editors, it shows more promising potential on supporting a conceptualization of role-concepts. Role-concepts refer to a concept which cannot be defined without mentioning other concepts. Examples include wife, husband, student, child, etc. Based on the theory, there are three categories for this concept. That is, a basic concept, a role-concept, and a role holder.

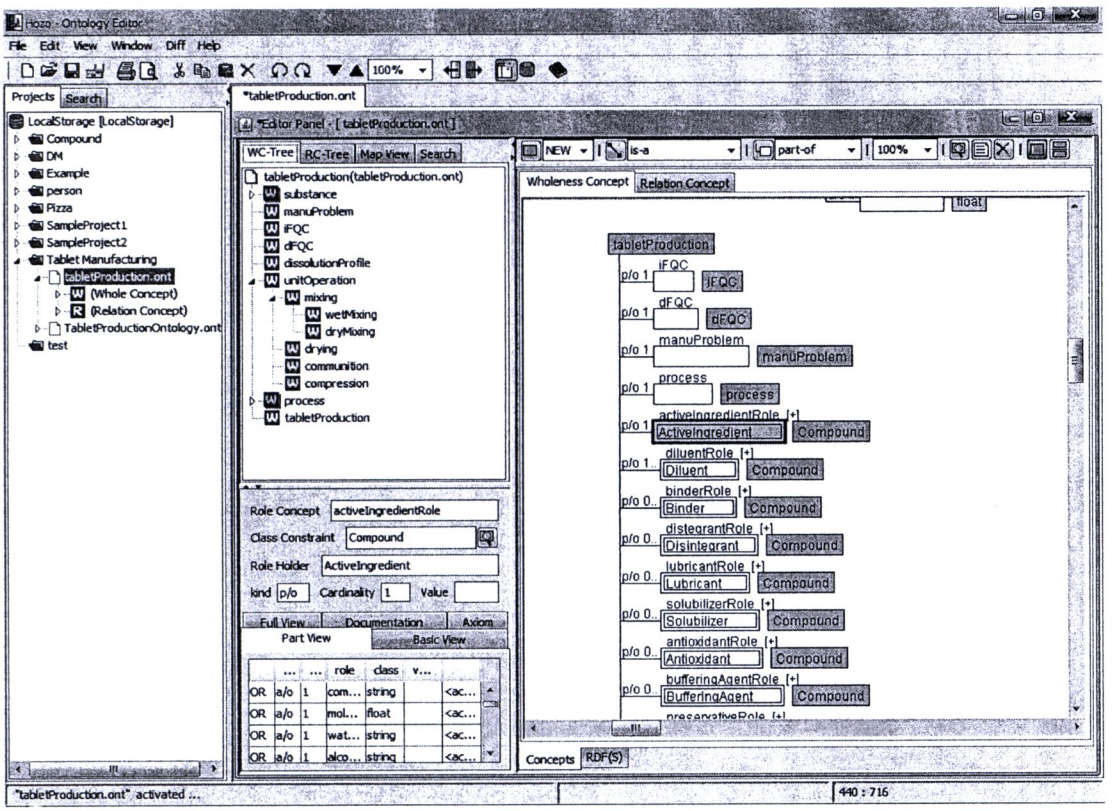

Figure 2.11 A snapshot of the interface of the Hozo ontology editor

A role-concept (Kozaki et al., 2000) represents a role which a thing plays in a specific context and it is defined with other concepts. On the other hand, a basic concept does not need other concepts for being defined. An entity of the basic concept that plays a role is called a role holder. For example in "a bicycle", its wheel plays the role as a front wheel ("a front wheel role") or a role that steers its body ("a steering role"), which is defined as a role-concept. A wheel that plays these roles is called "a front wheel" and "a steering wheel", respectively, which are role holders. For the enabling of role-concepts, the ontologies particularly become more flexible since the specification of role and concept can be separately designed.

2.5 Expert System

Expert system has a wide divergence of definition. For example, Sell P. S. (Sell, 1985) has defined an expert system as "an expert system is a knowledge-based system that emulates expert thought to solve significant problems in a particular domain of expertise". Patridge and Hussein also gave a definition of an expert system as "an expert system is a computer program that draws on knowledge of human experts captured in a knowledge base to solve problems that normally require human expertise" (Partridge and Hussein, 1994).

In its ordinary form, an expert system has three main components: 1) an interface and two-way communication device between user and system; 2) a knowledge base where all the knowledge pertaining to the domain is stored; and 3) an inference engine where the knowledge is extracted and manipulated to solve the problem at hand.

An inference engine is a computer program that attempts to derive answers from a knowledge base. An inference engine is created based on the conceptual quote from R. Descartes that "Each problem that I solved became a rule which served afterwards to solve other problems. (Clarke, 2006)" An inference engine is a key of intelligent software within an expert system using for reasoning about the information in the knowledge base for the ultimate purpose of formulating new conclusions. Inference engines are considered to be a special case of reasoning engines, which can use more general methods of reasoning.

Expert systems exploiting in pharmaceutical product development are mostly developed for design a drug formulation. In manual designing a formulation, the formulators must take into account that the properties of the active ingredient as well

as possible chemical interactions between it and added excipients since these may cause a chemical instability and a physical instability. Knowledge or pharmaceutical expertise given in the system can assist the formulators to solve or prevent problems which need manual intention. General benefits of a pharmaceutical expert system are listed below (Rowe, 1993a; Rowe, 1999):

1. Knowledge protection and availability: The existence of coherent and durable knowledge base is not affected by staff turnover. Number of experts systems is helpful for easy availability of information and the rapid access of physical and chemical data of drug and excipients which reduce the time spends for searching the literature.

2. Consistency: All system generates robust formulation with increased certainty and consistency and this is considered as a distinct benefit where the regulatory issues are important.

3. Training aids: All the system has been used to provide training for both novice and experienced formulator.

4. Speed of development: Reduction in the duration of the formulation process has been reported by many formulators who are using expert system.

5. Cost saving: It can be achieved by reducing a development time and more effective utilization of ingredient.

6. Freeing the experts: The implementation of expert system in formulation has inevitable allowed expert formulator to spend more time for innovation.

7. Improved the communication: Expert systems in a company have provided a common platform from which to discuss and manage changes in working practice and to identify those critical areas where the research is required.

8. Improvement in formulation: It provides opportunities to improve the formulation which may be extend product life of existing drug.

Literature survey reveals that following expert systems are become integral part of product development strategy in various dosage forms. Several expert systems have been implemented in pharmaceutical product formulation since 1989. They are categorized into two groups based on their recommendation criteria, namely a pure production-rule based system and a rule with knowledge based system.

2.5.1 Pure production-rule based system

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

There are two types of production-rules which are a atomic rule and a composite rule. An atomic rule is a simple rule which represents in if-then form. For multiple conditions and actions, two or more atomic rules can be integrated to form up a composite rule. Since there is a lot of knowledge used in pharmaceutical product development, such as properties of drugs, properties of excipients, incompatibility between ingredients in drug formulations, properties of drugs and manufacturing processes, production rules complexly become sophisticated. It is noted that 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 (Striker et al., 1994; Striker et al., 1991) was developed by personnel of Cadila Laboratory Ltd. (Ahmedabad, India). It has been designed to

formulate tablets for active ingredients based on their physical, chemical and biologically inter-related properties. It was written in PROLOG with 300 rules. It is structured in two knowledge bases stored in a spread-sheet format. Two knowledge bases include 1) the selection of excipients for active ingredients based on their physical, chemical and biological properties; and 2) interaction between ingredients. This system can identify most compatible excipients for the active ingredient. It is reported to have reduced the development time for a new drug formulation by 35%.

The Capsugel system (Bateman et al., 1996) was implemented to aid the formulation of hard gelatin capsules. This system was developed by University of London (UK) supported by Capsugel and University of Kyoto (Japan) and Marryland (USA). It uses production rule with a decision tree implemented in 'C', coupled with user interface through which the user can access both the database and develop new formulation. In this system, all necessary inputs have been design in questionnaire form. It requires the information on physical properties of active ingredient (e.g. dose, particle size, solubility, wettability, bulk density, melting point etc.), compatibility with excipients and the specific manufacturing conditions used by the user. The systems provides an output package that includes all the necessary information required for processing and filling of powder, capsule size, statistical optimize formulation, specification of excipients, recommended test for quality of product and complete documentation of formulated product.

Both systems return outputs in term of ingredient list and their amount. These systems apply rules with information from the database to formulate drugs. In a summary, the pure production-rule based systems are easy for development, but they;

in fact, cannot handle relations among knowledge in the deep level for complex formulations.

2.5.2 Rule with knowledge based system

This group of systems uses knowledge representation to store pharmaceutical knowledge and apply together with a set of production rules. In a mean time, two knowledge representations are applied: frame and ontology representation.

2.5.2.1 Frame based system

Frame is a structure that represents knowledge on a limited aspect of objects. With the use of frame representation, knowledge in pharmaceutical product development can be represented in a deeper level. Pharmaceutical expert systems in this group include Galenical, Sanofi, Zeneca, and Boots.

The Galenical system (Frank et al., 1997; Lai, 1995; Lai, 1996) was implemented by personnel at the Department of Pharmaceutics and Biopharmaceuticals of Medial Informatics at the University of Heidelberg (Germany). It has been designed to assist the development of many formulations (e.g. aerosols, tablets, capsules, intravenous injection), using chemical and physical properties of an active drug. It was originally implemented in "C" and recently upgraded using SMALLTALK. The output of this system are 1) formulation 2) production method 3) recommended packaging and 4) prediction of production properties.

The Sanofi system (Rowe, 1998) has been designed for formulating hard gelatin capsules based on preformulation study of the active ingredients. It was

implemented using Product Formulation Expert System (PFES) to generate one first-pass capsule formulation with as many subsequent formulations.

The Zeneca system (Rowe, 1993b; Rowe, 1995) is designed for formulating tablets, parenterals and film coatings. In this system, two experts are stored in frame, one with extensive heuristic knowledge and the other with extensive researcher knowledge. The system is fully interactive with users, requiring specific input data on the active ingredient to recommend a list of formulations with predicted properties.

The Boots (Wood, 1991) system is designed to assist the formulation of sun oils, creams and lotions. Despite it was not developed by pharmaceutical research group, it can be seen that frame representations can be applied to a lot of formulation types compared to the above mentioned output. Since knowledge represented in the frame is restricted to slots which represent concepts in detail, it affects the simpler and clearer production rules. This system is the only system which provides details of costing and quantitative benefits.

In a summary, frame representation is widely used in many expert systems because it gives a sufficient and easily accessible knowledge for systems. However, knowledge represented in frame has expressive limits about contiguous relations for deep knowledge since it cannot handle relations among concepts properly. Additionally, it is difficult to manage explicit complex relations separated from the frame.

2.5.2.2 Ontology based system

In the recent work on pharmaceutical supporting systems, domain knowledge is represented in ontology. Musen discussed about a common goal in developing

ontologies for representing domain knowledge in the systems that "sharing common understanding of the structure of information among people or software agents. (Musen, 1992)"

They include OntoReg and Ontological informatics infrastructure for pharmaceutical product development and manufacturing.

The OntoReg (Sesan et al., 2009) is a ontological framework for automated regulatory compliance in pharmaceutical manufacturing. It has been developed for assisting drug manufacturers by giving guidelines on manufacturing process. OntoReg encapsulates the process and regulation knowledge in OWL ontology and uses axioms and rules as means to enforce pharmaceutical regulatory guidelines. In the current status, its ontology is in development process. Developers claim that the system is crucial to be applying to real industrial processes for its ontology to evolve and be refined.

The Ontological informatics infrastructure for pharmaceutical product development and manufacturing (Venkatasubramanian et al., 2006) has been developed by personnel of School of chemical engineering, Purdue University (USA) supported with Bayer technology and engineering (Shanghai) Co. Ltd. (China). They aim to develop an ontological information-centric infrastructure to support product and development in the pharmaceutical manufacturing domain. In this work, ontology is used to generate a model of the related information, while Semantic Web provides a general framework for implementing the infrastructure. The model and infrastructure are together used throughout the system to recommend guidelines for every process in pharmaceutical product development and manufacturing.

For a summary, recently ontology has been applied to represent domain knowledge in pharmaceutical supporting systems. It enables the sharing of knowledge, the re-use of knowledge and the better engineering of knowledge based system with respect to acquisition, verification and maintenance. It can be claimed that ontology representation not only retains equal abilities to frame representation, but also it gains additional benefits. However, there is no a pharmaceutical expert system which uses ontology to help on design a drug formulation by far. Moreover, all mentioned systems have been designed to formulate a new drug formulation, not a generic drug which is a large economic pharmaceutical product in Thailand. In addition, their outputs are all provided with only a list of excipients, their amount, and some attributes of productions such as the capsule size and the tablet diameter. These data are insufficient for novice pharmacists in actual drug production because the novice one also needs production instructions in details for guidelines. Moreover, there is no expert system that can formulate an herbal tablet which is one of the most specific and well-known localized wisdom of Thai culture.