CHAPTER I
INTRODUCTION

It is now widely recognized that quality assurance of drugs in third world countries is an oft neglected issue. To be commercially competitive with other products, quality assurance procedures may be compromised in some cases such as a drug product low cost and time desire lead to an inadequate control on the synthetic, manufacturing process, and an final check of quality is always occurred. Sometimes lack of quality assurance can have dire consequences as result of drug products [1]. In addition to the content and purity of a drug formulation, its ability to release the required amount of drug within a favored time is an important factor in drug product quality. The release characteristics of the dosage form play an important role in the availability of a drug, either in terms of its systemic availability or, where appropriate, its local action in the gastrointestinal tract. As chemical property changes the changing of physical property always occurs during product processing and storing such as crystallization from amorphous state. This physical change leads drug product to poor dissolution rate. The quality excipients used (such as fillers, binders, lubricants, disintegrants, surfactants) in manufacturing, the quality of the process, and the storage condition itself are consequently of great importance to drug quality.

The drug under investigation in this study was aspirin, which is used as an analgesic, antipyretic, and anti-inflammatory agent. Aspirin belongs to the group of non-steroidal anti-inflammatory drugs commonly abbreviated as NSAIDs. Recent studies concluded that aspirin also reduced the risk of heart attack and coronary heart diseases [2]. Aspirin has the unique standing in the medical world of still being the most widely used drug, even with advent of modern, highly potent therapeutic agents. It is in the World Health Organization's list of essential drug [3]. Furthermore, aspirin is the basic drug used in Cambodia. Aspirin is produced in many formulations. Uncoated aspirin tablet is one of the most popular formulations, because of its simple production and low cost. This solid dosage form of aspirin is used in oral products. For its stability, aspirin undergoes hydrolytic degradation, which is main degradation pathway. This is due to the

fact that carboxylic acid ester of aspirin is susceptible to hydrolysis. The degradation of aspirin in the pH range about 5-8 is independent of pH [4]. The major reaction mechanism in this pH range is intramolecular general base catalysis of the attack by water on the acetyl ester functional group by the neighboring carboxylate group. Aspirin hydrolyses to salicylic acid and acetic acid (Figure 6).

Due to its susceptible decomposition, the major unacceptable quality of aspirin tablets can be occurred because the degradation of products. This phenomenon can happen during the manufacture or after a certain period of storing and using of the grade variability of starting material or impurity of active ingredient for its formulation.

Nowadays, the uncoated aspirin tablets are widely used as over the counter (OTC) medications in Cambodia. They have now been marketed under many trade names and many sources. The majority are imported for example, Aspirin (Golden Cup Phar.), Aspirin (Vysali Phar. Ltd), ASLAC (Sea Pharm), ASPACO B.P.O (Burapha Dispensary), Aspirin (S.S.P. Lab.), Jamjai (Osotspa Co.,Ltd). Only one trade name is found locally produced which is Acide Acetylsalicylique (Cambodian Pharmaceutical Enterprise). However, there are legal and illegal imports among imported products [5]. So far, there has been no study on aspirin qualities. How quality of each uncoated aspirin tablet which are available in market has still been a question.

For Cambodian health care system, the impact of many years of disruption and genocide on the health care system was devastating. Only 50 doctors were left in 1979. Health facilities were damaged and equipment non-functional. In order to develop an accessible and affordable system, the Government decided to redevelop the public health system with a new structure. The previous system aimed at establishing either a provincial hospital in each province or a district hospital in every district, based on the existing administrative districts, and a clinic in every commune. The new policy which was agreed in 1995 and embodied in the 'coverage plan', defined 67 new 'operational districts' based on population. The policy defines a two tier service structure (plus national referral hospitals), with a referral hospital in each operational district and then health centers serving a catchment population of about 10,000 people. Where population

density is low and there are geographical barriers to access, districts can also establish health posts which are smaller than health centers [6], [11]. In year 2001, there are 108 non-government organizations (NGOs) working in health sectors. There are 382 private clinics and hospitals registered, whereas 70% of providers are not registered. Household spending on health in year 2000 was 11% of GDP, or 80% of all health expenditures [5].

In Cambodian pharmaceutical sector, public utilizes a centralized procurement and distribution system. Donor-funded pilot contracts out management of public health facilities to private organizations. The total pharmaceutical expenditures of year 2000 were 31.46 million US$, which is divided to 57% households, 25% Donor, and 18% Ministry of Health. There are two sectors of drug supply, private sector and public sector. For private sector, the distribution of drugs has been done through pharmaceuticals importers, wholesalers, and private pharmacies. As of October 2000, the numbers of licensed pharmacies countrywide were 892 and the illegal outlets were estimated to be around 2,800 (75%). The country has one joint-venture pharmaceutical industry with China and six others private pharmaceutical industries producing oral dosage form. They covered only 5-10% of the need in medicines for the whole population. There are currently seven local manufacturing plants, but two of them are dealing only with drugs repackaging. Most of drugs needed are covered by imported products which total yearly cost is roughly 12 millions US$. For public sector, Ministry of Health has a Central Medical Store which distributes drug to all 73 referral hospitals and more than 700 health centers countrywide. Drug procurement and drug distribution are still under a centralized system, which face some constraints. For example, shortfall and excess of drugs often occur. The policy of the Ministry of Health is now toward decentralization of the procurement system to lower levels as well as the creation of a Government Purchasing Center [7].

Ministry of Health (MOH) in Cambodia has three Directorate Generals; Directorate General for Administration and Finance, Directorate General for Health, and Directorate General of Inspection. The Department of Drugs and Food (DDF) is a regulatory agency under the Directorate General for Health that is mandated to ensure

the safety, efficacy, quality of drug and medical device. Its duty extends to the quality of food and cosmetic. The organization chart is shown in Appendix A and B.

For health insurance in Cambodia, the Constitution of Cambodia year 1993 adopts health international principles: "The health of the people shall be guaranteed. The State shall give full consideration to disease prevention and medical treatment. Poor citizens shall receive free medical consultation in public hospitals, infirmaries and maternities". Sadly, such guarantees mean little to people whose right to health is being violated daily. In spite of international efforts, the country has not recovered from the Pol Pot regime's tragic legacy. In September 2000, the Asian Legal Resource Center conducted an investigation into Cambodia's health care system. It confirmed the poor state of the Cambodian people's health and found that this was due to a lack of funds, the poor quality of medical service. The average salary of a Cambodian doctor in a public hospital is about US$ 20 per month. Consequently, doctors in public hospitals neglect to see patients with no money, even in the emergency room. Medical staffs are unevenly distributed throughout the country, 87 percent of people live in the country's rural areas but only 14 percent of Cambodia's medical staff are base there. Some staffs outside urban areas are not enough literate. The lack of health care professionals in the countryside has implications for rural poverty [8]. The among of out of pocket expenditure on health in Cambodia is very high, about 11% of rural expenditure is for health. Among the poorest this rises to 28%. This is unusually high for developing countries and forms a major burden, with health expenditure a common cause of poverty. WHO estimates that per capita health expenditure is US$ 20 or more (a 1996 survey found US$ 31 per capita). In 1998, the Government spent about US$ 1 per capita and international development agencies funded another US$ 4 per capita. The utilization of public sector health services is generally low, the average number of contacts with public sector health providers is only 0.3 per people per year. While this partly reflects limited geographical access, there are also problems of low perceived quality of service [6].

In Phnom Penh, there is a mix of inadequate quality drugs with adequate quality drugs. The inadequate quality drugs include counterfeit drugs, decomposition of the active ingredient in drugs due to high temperature and humidity of storage, and poor quality assurance during the manufacture [9]. Characteristics such as physical appearance, cost of the tablet and packaging reliably predicted authenticity [10]. Thus the unacceptable quality drugs are always used by physicians and patients without intending.

For drug quality problem, after the liberation of Cambodia from the genocide Pol Pot (1975–79), everything had to be started virtually from scratch. In the pharmaceutical sector, most dealers had little knowledge of medicines. Drugs from unknown sources were frequently available in most Cambodian markets. Counterfeit and substandard drugs have mostly entered the supply system through illegal outlets. Along the border there are eight official checkpoints but a large number of cross-border entry points facilitate the smuggling of any kinds of pharmaceuticals into the country. Due to lack of education, human resources, inefficacy of law enforcement and lack of equipment and capacity for quality testing, people are easily cheated by counterfeit and/or substandard drugs. In Cambodia, only drug products which have been registered by the Department of Drugs and Food (DDF) will be authorized to be imported, manufactured, sold by retail pharmacy, displayed and dispensed under conditions required in the license granted to undertake these activities. According to the report of DDF, around 5,000 products are available in the market but nearly 40% are not registered. The dangerous problem of drug is pharmaceutical anarchy and counterfeit drugs. A lot of effort has been put by Ministry of Health to combat the anarchy in the pharmaceutical sector such as the development and implementation of pharmaceutical law and regulations. But so far these efforts are still unsuccessful because of the weakness of law enforcement, the weak education campaign to increase the awareness of public, the poverty of Cambodian people, the insufficient number of drug inspectors and the lack of budget for them, and the lack of good collaboration between concerned regulatory agencies. Even though counterfeit and/or substandard drugs have been freely available in Cambodia for many

years, very few study or survey have been conducted to indicate the severity of problem throughout the country. Sokhon Chroeng & Phirun Ung [5] reported on Cambodian drug market study of MOH in Conference 2001 on Strategies for Enhancing Access to Medicines (SEAM) that overall failure rate of 13.5% of drug quality was found, and 50% of drugs are not registered. The failure rate of drugs is 5.2% of the registered drug and 22.3% of unregistered drug. In a study of MOH with WHO on counterfeit drugs in Cambodia year 2000 reported that there are 6.12% failed in the quality test among the registered drugs and 20.86% failed among the unregistered samples. This study also found 13.04% counterfeit drugs [7]. The reality of the counterfeit drug and the unacceptable quality drug problem in Cambodia could be worst than the results revealed by these studies. This is because the first choice of most poor Cambodians (at least 80%) has very limited access to the legal drugstores. Hence, the most common practice among such people is to obtain their requirements from small drug shops. Most of them are unlicensed outlets, where presence of counterfeit drugs and unacceptable quality drugs are very high.

In this study, to determine the drug quality, the uncoated aspirin tablets are studied on the aspects of tablet properties, label amount, weight variation, hardness, friability, disintegration time, and dissolution. The studies are carried out on each sample collected from drugstores in Phnom Penh City, Cambodia. The result obtained from quality assessment experiments are compared with the limits of in USP XX 1980, USP XXV 2002, BP 1993, and other requirements.

The objective of this study is to examine the quality of the uncoated aspirin tablets obtained from drugstores in Phnom Penh, Cambodia, between October and November 2002, and also to assess the factors relating to aspirin quality.