CHAPTER I

INTRODUCTION

Rationale

It is generally accepted that the dissolution of a drug from a formulation may affect both its absorption and therapeutic characteristics. Since it is axiomatic that the drug must be in dissolved state before being absorbed into blood steam. Dissolution of the drug occurs not only from the fine particles but also from the granules and the intact tablets. It is concluded that the dissolution rate of the drug can be a rate - determining step in the absorption process. Consequently, dissolution rate may affect the onset, intensity and duration of biological response.

The dissolution of a drug from a tablet can be affected by many factors and have been reported by several investigators[1]. Various factors such as production process, particle size, granule size and distribution, nature and quantity of diluent, binder, disintegrant, surfactant, lubricant, compressional force, dissolution medium and storage condition have been shown to influence the dissolution rate. In the production of tablets, additives have to be included as a part of tablet formulations in order to enhance the physical appearance, improve stability, impart satisfactory compression characteristics and give additional desirable physical characteristics to the finished product[2]. As a result, care must be taken in the selection and comparison of additives

to use in order to ensure that physiological availability and therapeutic efficacy of the drugs will not be hindered. The variation of dissolution behaviours can exists when formulation and processing factors are altered. The dissolution rate of the same active ingredient from the solid dosage forms of several manufactures may be significantly different mostly due to the differences of formulations.

Although, in - vitro dissolution data itself can not be used as a sole predictor of in - vivo performance of a dosage form. However, dissolution tests are useful and valid, as a quality control procedure, in product development for the rejection of unsuitable formulations, in the detection of lot to lot variation, and in the demonstration of differences among products of various manufacturers. Therefore, since 1970 USP and NF have provided procedures for dissolution testing. Dissolution time of a given tablet formulation must meet the requirement as specified in the individual monograph[3,4]. Although, dissolution tests are more useful and valid than the traditional tablet disintegration test. But most of local pharmaceutical manufacturers at the moment are still rely on tablet disintegration test as an indicator of drug availability of the newly developed formula.

Therefore, in product development, the need for better understanding of the effect of additives, incorporated in the tablet formulation, on the availability of the tablet is deemed necessary. Dissolution tests would rather be considered as the closest to real indicator of pharmaceutical availability of the

newly developed formula than other tests.

Purposes of the Study

The scope of this research is to perform comparative studies of the effects of various additives used in tablet formulation on the dissolution behaviour of dipyrone tablet. The effect of other relevant factor such as additives concentrations, hardness of the tablets etc. on dissolution pattern of dipyrone were also studied.

The reason of selection dipyrone as the model drug, is due to the widespread used of dipyrone as an analgesic and antipyretic in the treatment of headache, pain due to biliary and renal colic, and pains such as that associated with neuralgia and rheumatism[5]. From previous study of Jantrarasakul et al.[6], the dissolution profiles of twenty commercial dipyrone tablets from different manufacturers possessed different dissolution characteristics. The time required for the tablets to release 90% of dipyrone ($t_{90\%}$) varies greatly among the twenty brands and ranged from 6.0 $\pm$ 1.1 minutes to 102.0 $\pm$ 12.0 minutes. It is concluded that different brands of dipyrone tablet labeled to have the same quantity of active ingredient might not have the same therapeutic efficiency due to their different dissolution characteristics, which in turn may be most probably caused by the different product formulations.

All the additives used in the experiments are commonly employed as a component of compressed tablet formula. The amount of additives used in this studies are also varied in the practical range.

The present studies were designed to persuade and facilitate the local tablet producers in order to develop their own product formulation by using the proper additives with an objective of optimizing the dissolution of dipyrone tablet.

Literature Reviews

There were many reports published in the literatures regarding the effect of formulation and processing factors on the dissolution rate of the active ingredients from compressed tablets, for example, the difference in dissolution rate of commercial phenobarbital tablets from 24 manufacturers was reported by Jacob and Plein[7]. Omray et al.[8] reported the difference in dissolution rate of commercial diazepam tablets from 10 manufacturers. The dissolution rate of active ingredient from compressed tablets of several manufacturers may be significantly mostly due to the differences of formulations.

Hirschon and Kornblum[9] studied the effects of excipients dilution and force of compression on dissolution of directly compacted quinazolinone compound tablets. They found that the greater the quantity of diluent, the higher was dissolution rate and a linear relationship was obtained when plotting $t_{50\%}$ versus tablet weight. But an increase of the compressional force provided divergent results, the larger the tablet size, the less effect compressional force had on the dissolution rate. They concluded that when formulation a tablet of a poorly water soluble drug, the following should be considered : optimum tablet size, hydrophilic

nature of diluents and optimum force of compression.

Omray et al.[8] studied the influence of six diluents on in - vitro release of diazepam through a fine tery - cot cloth. The diluents used were lactose, starch, manitol, calcium carbonate, microcrystalline cellulose (Avicel pH 105) and a combination of lactose and microcrystalline cellulose. Lactose and starch were found to release the total drug incorporated within a very short peroid.

Marlowe and Shangraw[10] prepared tablets of sodium salicylate by wet granulation using either lactose or a mixture of lactose and corn starch as filler. They found that the presence of starch dramatically increased the dissolution rate of the active ingredient.

Levy et al.[11] found that starch has a favorable influence on the dissolution rate of tablets prepared by double compression. Increasing the starch content of granules from 5% to 20% resulted in an increase in the dissolution rate of salicylic acid. This result agreed with the report of Baveja and Kakkar[12] in which sulfadimidine and wheat starch were used.

The effect of different granulating agents on the rate of dissolution of phenobarbital tablets has been studied by Solvang and Finholt[13]. Phenobarbital tablets prepared with gelatin as granulating agent were found to dissolve much faster in human gastric juice than tablets prepared with sodium carboxymethylcellulose or polyethylene glycol 6000 as binders, probably because gelatin makes the originally hydrophobic surface of drug particles hydrophilic

whereas sodium carboxymethylcellulose at the pH of dissolution medium is converted into the less hydrophilic free acid and polyethylene glycol 6000 forms a complex of reduced solubility with phenobarbital.

Jacob and Plein[14] studied the effect of various binders such as gelatin, acacia, ethylcellulose, hydroxyethylcellulose. They found that increase in binder concentration and hardness of tablet resulted in a decrease in the dissolution rates of phenobarbital tablets. Selection of binder, its concentration and hardness at which tablets were compressed, were important factors which should be properly controlled.

Oudtshoorn et al.[15] showed that sulphadimidine tablets using methylcellulose as a binding agent dissolved faster than those using starch paste or gelatin mucilage.

Sakr and Elsabbagh[16] formulated tablet of nicotinic acid by using acacia and sodium alginate as the binder. It was found that acacia had little or no effect on dissolution time of nicotinic acid tablet while sodium alginate had a marked delaying effect on the dissolution rate. As the amount of sodium alginate was increased in the formula, the rate of dissolution decreased.

The effects of binder concentration, compressional force, granule size on release of erythrosine from lactose compacts was reported by Shubair and Dingwall[17]. They found that the rate of in - vitro release of erythrosine from compacts of lactose granulated with starch mucilage was reduced by increasing binder

concentration and by increasing compressional force. But it was virtually unaffected by granule sizes. Effects produced by interaction of all three factors in combination were found to be non-significant.

Chalmers and Elworthy[18] studied the effect of polyvinylpyrrolidone (PVP) on the dissolution rate of oxytetracycline dihydrate tablet. An increased concentration of PVP in the binder solution decreased the rate of tablet dissolution. Although the volume of granulating solution apparently controlled the granule size, it did not significantly alter the tablet dissolution, when the amount of PVP was constant.

Shukla and Verma[19] reported that paracetamol tablets prepared by wet granulation using different binding agents (sodium alginate 4%, starch 10%, carboxymethyl cellulose (C.M.C.) 4%, gelatin 4%, and acacia 4%). The tablets prepared with C.M.C. release 50% of the drug within 17 minutes, while those containing sodium alginate, gelatin, acacia and starch took 19, 22.5, 30 and 37 minutes respectively to release 50% drug.

The tablet disintegrants : alpha-cellulose, Veegum and starch were used by Yen[20]. Only starch was considered satisfactory. It was found that the active ingredient, triamterene, was absorbed by the Veegum and therefore the drug was not totally available.

Mendell[21] studied the three most commonly used tablet disintegrants : corn starch, alginic acid, and Avicel ® by comparing

with carboxymethyl starch for rates of disintegration. In the direct compression method, carboxymethyl starch was shown to be better disintegrant than all others for both water-soluble and water-insoluble active ingredients. In all cases of wet granulation, carboxymethyl starch evidenced superiority to the other disintegrants and the method of incorporation appeared to have little affect in the formulations prepared.

Rubinstein and Price[22] studied the effect of five tablet disintegrants on the bioavailability of frusemide from tablets. Tablets of frusemide 40 mg. were prepared containing approximately 10% W/W of the disintegrants, Explotab, Polyplasdone XL, Amberite IRP 88, Maize starch B.P. and Elcema P 100. No quantitative relation was found between disintegration time and dissolution rate or bioavailability. Maize starch and Elcema P 100 rendered the drug significantly less bioavailable than other three disintegrants, the tablets containing Explotab gave the highest bioavailability. The results indicated that the choice of disintegrant can significant affect bioavailability of the final product.

Four tablet disintegrants : a relatively insoluble sodium carboxymethylcellulose, casein formaldehyde, calcium carboxymethylcellulose and a cross-linked polyvinylpyrrolidone have been evaluated by Khan and Rooke[23]. Three widely used disintegrants, sodium carboxymethyl cellulose, sodium starch glycolate and a cation exchange resin were included for comparison. The effect of compressional pressure on the disintegration and dissolution behaviours of a soluble and an insoluble system containing different

disintegrants was examined. The results showed that disintegrant type can have a pronounced effect upon the relationship between compressional pressure and dissolution efficiency.

Levy and Gumtow[24] found that 3% magnesium stearate retarded the dissolution rate of salicylic acid from tablets prepared by double compression, while the surface active lubricant sodium lauryl sulfate markedly enhanced the dissolution rate.

Ahmed and Enever[25] studied the influence of the hydrophobic lubricant magnesium stearate on the release of the sparingly-soluble drug sulphadiazine from tablets. An increase in the lubricant concentration from 0 to 0.5% W/W caused a significant in disintegration time and decreased in dissolution rate due to the hydrophobic lubricant coating the drug particles.

Iranloye and Parrott[26] found that an increase in the concentration from 0.1 to 5% of calcium stearate, glyceryl monostearate, magnesium stearate and stearic acid progressively slowed the dissolution rate. While an increase in the concentration from 0.1 to 5% of talc and polyethylene glycol 4000 did not affect the dissolution rate of compressed disks of salicylic acid, aspirin and an equimolar mixture of aspirin and salicylic acid. They also found that the compression forces from 450 to 9100 kg. had no effect on dissolution rates. With 5% starch incorporated into an equimolar mixture of aspirin and salicylic acid, the dissolution rates were independent of compression forces from 910 to 9100 kg.

Kitazawa et al.[27] studied the effect of hardness on

disintegration and dissolution characteristics of uncoated caffeine tablets made at eight different pressure levels. The hardness governed the dissolution over all the stages from tablet to the smallest particles after the breakage by disintegration.