CHAPTER 1

INTRODUCTION

Valproic acid (VPA) is one of the major antiepileptic drugs that was demonstrated to have a broad spectrum of anticonvulsant activity. However, because of its poor partitioning across the blood-brain barrier, VPA exerts a moderately anticonvulsant activity. Moreover, it has two major side effects including teratogenicity and hepatotoxicity (1,2). Together with the fact that VPA is less potent than other three established antiepileptic drugs; phenobarbital, phenytoin and carbamazepine, development of new derivatives of VPA with higher potency but lower toxicity is needed (3).

In Thailand, Boonardt Saisorn and co-workers, staffs in the department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Chulalongkorn University have synthesized valproic acid analogues by modifying the carboxyl group. N-(2-propylpentanoyl) urea (Valproyl urea, VPU) is one of the new VPA analogues, which partially resembled the structure of barbiturate ring and VPA in the same molecule (Figure 1) (4,5).

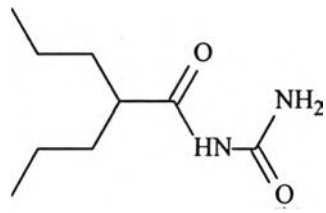

Figure 1: Molecular structure of N-(2-propylpentanoyl) urea

The anticonvulsant activity of VPU in mice and rats has been studied by Thongchai Sooksawate (1). The study demonstrated that, in comparison to VPA, VPU exerted higher potency, greater safety margin and lower unwanted side effects. Further studies by Boonyong Tantisira and co-workers (2,6) and Tipsuchon Chunngam (7) confirm a good prospect of being a potent broad spectrum antiepileptic drug with higher anticonvulsant activity and higher relative safety margin than its parent compound, VPA.

Embryotoxicity in rats has been conducted by Roongruedee Meesomboon and co-workers (8). The study suggested that VPU produced less developmental toxicity than VPA did.

Because of the sufficient pharmacologic promise in animal models, VPU is an appropriate substance to enter a preformulation program. The preformulation study includes numerous investigations that reveal physicochemical properties of the new compound. A thorough understanding of these properties may provide a rationale for formulation design (9,10).

Preformulation is a branch of the pharmaceutical sciences applied to work done on a compound, which is considered for development by an organization, which can be either an innovator, or generic organization. Preformulation is different in these two cases (11). Most of the preformulation works in Thailand is considered to be generic approach, working with an already existing drug molecule. Although preformulation is not confined to innovator organization, the scope of the study for drug development in Thailand is limited. This is a good opportunity to introduce a systematic study of new drug development in Thailand.

Many pharmaceutical solid can exist in several internal structures, such as polymorph, amorphous, solvates and hydrates. Such forms may present different physicochemical properties that could affect product performance in solid-state dosage forms (12,13,14). The internal structure alteration may affect solubility (15,16,17) dissolution rate (15,17,18) and solid state stability (19,20). Solid drug substances display a wide and largely unpredictable variety of solid state properties. Therefore, increased understanding of solid state properties allows a rationale for formulation design and processing (21,22)

The primary aim of this study is to characterize the solid state chemistry and physiochemical properties of N-(2-propylpentanoyl) urea (VPU), which is an essential part of preformulation studies.

The specific objectives of this study were:

1. To investigate the possibility of VPU existence in various solid state forms such as polymorph, solvate, hydrate and amorphous.
2. To study the solid state chemical properties of VPU in each form that may exist.
3. To determine the solid state stability of VPU on the form(s) found emphasizing on properties which are dependent on the internal structure alteration of solid.