

## 以 TPGS 作為微乳基劑之相圖研究與藥學應用

### Studies on the Phase Diagrams of TPGS Based Microemulsion Systems and Their Pharmaceutical Applications

#### 中文摘要

本論文包含兩部分的研究：第一部分為以 TPGS 作為微乳基劑之相圖研究，第二部分為 Fenofibrate 自發性微乳化藥物傳輸系統之物性解析。

在第一部分的研究中，利用中鏈型三酸甘油酯 (Medium Chain Triglyceride) (商品名為 Captex 300) 作為油相、去離子水作為水相以及 D- $\alpha$ -Tocopheryl polyethylene glycol 1000 succinate (TPGS) 作為界面活性劑所形成的微乳基劑可以作為蛋白質藥物或水難溶性藥物的載體。藉由擬三相圖 (Pseudo-ternary Phase Diagrams) 的建立來瞭解中鏈型三酸甘油酯、去離子水及 TPGS 為主要界面活性劑配合聚醇山梨酯 (Polysorbates) (如 Tween 20、Tween 40、Tween 60 及 Tween 80) 為輔助界面活性劑或聚乙二醇 (Polyethylene Glycol) (如 PEG 400 及 PEG 600) 及多醇類 (Polyols) (如乙二醇、1,2-丙二醇、1,3-丙二醇、1,3-丁二醇、1,4-丁二醇及甘油) 作為共界面活性劑所形成的微乳基劑之相變化。TPGS 與聚醇山梨酯、聚乙二醇或多醇類以 4/1、2/1、1/1、1/2 及 1/4 之重量比例混合。當 TPGS 為唯一之界面活性劑組成時，水-Captex 300-TPGS 微乳基劑系統之相圖顯示系統無法形成較大範圍的單一相均質系統。當 TPGS 與聚醇山梨酯依不同比例混合為界面活性劑組成時，水-Captex 300-TPGS-聚醇山梨酯微乳基劑系統之相圖顯示系統可以形成較大範圍的單一相均質系統；此單一相均質系統包括微乳相或凝膠相且其各相系的範圍受到界面活性劑組成及比例所影響。利用多醇類作為共界面活性劑所形成的微乳基劑系統之相圖顯示多醇類對於單一相均質系統的影響程度小。但是，多醇類的含量組成會影響到此單一相均質系統的範圍大小；亦即多醇類含量愈高，單一相均質系統的範圍就愈小，且減小的趨勢是往相圖的界面活性劑-水的軸線趨近，顯示系統中若多醇類的含量增加將會減少油相的乳化總量。凝膠相的範圍亦會隨著系統中的多醇類含量增加而減少。如多醇類未與 TPGS 共同混合使用，將無法有效的將 Captex 300 乳化形成單一相均質系統。

第二部分的研究屬於第一部分的應用，其目的在於建立及解析自發性微乳化藥物傳輸系統作為難溶性藥物的傳輸載體。選用的難溶性藥物為 Fenofibrate (為一有效的降血脂藥物) 作為模式藥，利用中鏈型三酸甘油酯及非離子型界面活性劑製備成自發性微乳化藥物傳輸系統；此一系統若接觸到水溶液或腸胃道液體會自發性乳化形成微乳化透明澄清之液體。所選用的油相為 Myritol 318，非離子型界面活性劑為 TPGS 及 Polysorbates (Tween 20 或 Tween 80)。當使用 TPGS/Tween 20 之重量比例為 1/4 時，可以得到具適當溶離速率的處方組成。經由體外溶離試驗

結果顯示：Fenofibrate 自發性微乳化藥物傳輸系統無論在 0.025M 的月桂酸鈉水溶液或水中均可以在 30 分鐘內完全釋出。但是對照處方 Tricor? tablets 及微粉化藥物分散系統於水中的溶離則受到限制。由本研究的結果顯示自發性微乳化藥物傳輸系統可以有效的作為難溶性藥物的載體 (fenofibrate 為例)，增進其溶離速率與溶離量，因此可以相對有效的提高其生體可用率。

## 英文摘要

This dissertation is composed of two parts of studies; the title of part I is “Studies on the Phase Diagrams of D- $\alpha$ -Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) Based Microemulsion Systems” and that of part II is “Physical Characterization of Self-Microemulsifying Drug Delivery System for Fenofibrate”.

Attempts in part I of the dissertation were to develop microemulsion systems using medium chain triglyceride (MCT), Captex 300, deionized water (H<sub>2</sub>O), and TPGS as surfactant for the oral delivery of protein drugs or poorly water soluble drugs. Pseudo-ternary phase diagrams were constructed to elucidate the phase behavior of systems composed of medium-chain triglyceride and water with TPGS as main surfactant, polysorbates (Tween 20, Tween 40, Tween 60 and Tween 80) as adjuvant surfactants, and polyethylene glycols (PEG 400 and PEG 600) and polyols (ethanediol, 1,2-propanediol, 1,3-propanediol, 1,3-butanediol, 1,4-butanediol and glycerin) as cosurfactants. The weight ratios of TPGS to Tweens, PEGs or polyols (K<sub>m</sub>) were set at 4/1, 2/1, 1/1, 1/2, and 1/4. The phase diagram for H<sub>2</sub>O/Captex 300/TPGS system reveals that when TPGS was used as a sole surfactant, it is not capable of producing isotropic solutions of water and Captex 300 over a wide range of the compositions. H<sub>2</sub>O/Captex 300/TPGS/Tweens systems with various K<sub>m</sub>, regardless of the adjuvant surfactant used were capable of producing an isotropic phase. The extension of microemulsion phase and the presence and extension of the gel phase were found to be dependent on the surfactant mixture. The phase diagrams of H<sub>2</sub>O/Captex 300/TPGS systems using polyols as cosurfactants demonstrate that the types of polyols have a slight effect on the region of existence of the microemulsions. Comparison between the isotropic regions for the polyols system reveals that as the relative concentration of polyols increase, the isotropic region decrease in size. This decrease is towards the surfactant mixture (S<sub>mix</sub>)-water axis indicating that as the relative concentration of polyols increases the maximum amount of oil solubilized decreases. The gel region decreased in size with the increase of polyols weight ratio. All polyols do not solubilized Captex 300 without using TPGS as surfactant.

The part II of this dissertation is the application of the studies of part I. Attempts in

part II of the dissertation were to develop and characterize the self-microemulsifying drug delivery systems (SMEDDSs) for poorly water soluble drugs. Fenofibrate (an effective agent for the treatment of various types of dyslipidemia) was selected as a model drug that was formulated in a Myritol 318 and nonionic surfactant mixtures of TPGS and polysorbates (Tween 20 or Tween 80), which exhibited self-microemulsifying characteristics under conditions of gentle agitation in an aqueous medium. Using TPGS/Tween 20 as the mixture of surfactant (Smix) at a Km value of 1/4 was found to yield the desired SMEDDSs for fenofibrate. In vitro dissolution studies illustrated that the release of fenofibrate from SMEDDSs was complete within 30 minutes either in 0.025 M SLS solution or water medium. But the release of fenofibrate from Tricor? tablets or micronized fenofibrate dispersion systems (MDSs) was limited in water medium. The present study also revealed that the self-microemulsified drug delivery system of poorly-water soluble drugs exemplified by fenofibrate increased their dissolution rate leading to enhance their bioavailability correspondingly.