ABSTRACT

A Pharmaceutical Study for Improvement of Bioavailability of Phytomenadione (Vitamin K1)

It is well established that the active ingredient in a solid dosage form must undergo dissolution in order to become available for absorption from the gastrointestinal tract. The rate of peroral absorption of a poorly water-soluble drug is often controlled by its dissolution rate in the fluid present at the absorption site. The poor dissolution rates and consequently, inadequate absorption characteristics of water insoluble drugs are long–standing problems confronting the pharmaceutical industry.

Vitamin K ("Koagulation" in German) is a group name for a number of related compounds, which have in common a methylated naphthoquinone ring structure, and which vary in the aliphatic side chain attached at the 3-position.

Vitamin K is soluble in fat and is produced in the body, by bacteria that naturally live in the gut. It is also commonly found in the diet, in green leafy vegetables and meat. Vitamin K acts in the liver and is essential for the production and activation of certain blood clotting factors.

Phytomenadione is similar to Vitamin K, which is found naturally in the body. It can be used as a supplement for natural vitamin k, in order to promote the production of clotting factors by the liver and prevent vitamin K deficiency bleeding.

Phytomenadione is absorbed primarily from the middle portions of the small intestine. Optimal absorption requires the presence of bile and pancreatic juice. Systemic availability following oral dosing is approximately 50%, with a wide range of interindividual variability.

The objective of this work was to improve the bioavailability of phytomenadione through increasing its water miscibility. In addition, the formulation of the drug as solid

solution tablets for oral use as well as solutions for parenteral use. Thus the work in this thesis is divided into three chapters.

Chapter I: Improvement of Water Miscibility of Phytomenadione.

In this chapter, liquisolid and solid solution Mixtures of phytomenadione with different pharmaceutical excipients and solvents were prepared. In addition, the miscibility of the drug with various solvents was studied.

Compatibility study of phytomenadione with the used excipients was studied.

The formulation- mathematical model of liquisolid systems, which is based on the flowable liquid retention potential of the constituent powders (Φ-value), was applied in this study.

Chapter II: Formulation and Stability Study of Phytomenadione Water Soluble Tablets and Parenteral Solutions.

In this chapter, phytomenadione was formulated into tablets. In addition, aqueous solutions of the drug for parenteral use were prepared namely, bicontinuous microemulsion and mixed micelle systems.

The prepared tablets were evaluated via determination of weight variation, tablet dimensions, content uniformity, hardness, friability, disintegration time and dissolution rate.

The best-chosen tablet formula was subjected to different types of coating and the coated tablets were evaluated.

The prepared parenteral solutions were evaluated via measuring drug content, viscosity, pH and rate of drug release, the particle size of the prepared microemulsions was determined.

Selected tablet, prepared microemulsion and mixed micelle formulations as well as the commercially available Konakione (Roche) tablets and mixed micelles were subjected to accelerated and photostability testing.

Chapter III: Bioequivalence Study of the Selected Phytomenadione Formulations.

In this chapter, In-vivo evaluation of the selected tablets in rabbits was done and the pharmacokinetic parameters were determined and compared to the commercially available Konakione (Roche) tablets.

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