Summary

Tropical Tablets

The development of tablet formualtions for use in tropical countries.

This Thesis deals with the development of tablet formulations for use in tropical countries. Many of the countries with a tropical climate are developing or Third World countries. In **Chapter 1** an introduction is given on the health care situation in general in these countries and more specifically on the situation of the pharmaceutical care. These problems are related to the general problems in Third World countries such as low income, undernourishment and low education level etc.

In **Chapter 1** a definition is given of the tropical climate. Also the influence of storage under tropical conditions on the physical, microbiological and chemical stability of drugs in general and tablets in particular is described. For stability testing for worldwide marketing the world is divided into four climatic zones. For each zone the average kinetic temperature and the average relative humidity are defined. For the hot and dry climate and the hot and humid climate the storage conditions are 31°C and <65% relative humidity, respectively 31°C and >65% relative humidity. The chemical stability of drugs is influenced negatively by the high storage temperature of the tropical climate. In developing countries tablets may be dispensed just wrapped in a piece of paper or not packaged at all. Without protective packaging tablets may sorb water during storage under tropical conditions, because tablets usually contain hygroscopic excipients, such as disintegrants. The physical quality of tablets may deteriorate due to this water sorption. The combination of high temperatures, the availability of water and suitable substrates, such as starch and lactose, creates favorable conditions for microorganisms to grow.

In **Chapter 2** the behaviour during compaction of corn, potato, rice and tapioca starch are compared. Rice starch proved to have better binding capacity than the three other starches. Moreover, rice starch is not susceptible to mixing with the lubricant magnesium stearate. This in sharp contrast to potato starch that has no binding capacity after mixing with magnesium stearate, due to the lubricant film formation. This difference can be ascribed to the small particle size and the angular particle shape of rice starch, as compared to potato starch, which has a round smooth particle shape. Due to this difference in particle size and shape, rice starch has poorer flow properties than potato starch. After granulation of rice starch, a product is obtained with good flow proprties and sufficient binding capacity after mixing with a lubricant. This product may be used as a filler binder in the preparation of tablets by direct compression. The four investigated starches had sufficient water sorption capacity to serve as a disintegrant.

In **Chapter 3** further investigations on the properties of rice starch after granulation are presented. Starch granulations were prepared with different techniques, in order to obtain granulations with different properties. The granule properties were analyzed in

relation to the sensitivity of the granulations to mixing with a lubricant. A linear relationship between the bulk density of the granulations and the lubricant sensitivity was found. The flowability of the granulations proved to be the determining factor. Poor flow properties, which are characterized by low bulk densities, retard or impede the formation of a lubricant film during mixing.

In the first part of the Thesis the properties of native excipients, which may be used as substitutes for the more commonly used products, were investigated. In the second part attention is paid to the stability of tablets. The relatively short consumers storage condition in tropical countries is considered in relation to the physical and microbiological stability of tablets.

In **Chapter 4** the influence of storage under tropical conditions on the microbiological quality of tablets is investigated. The investigation of the microbiological quality of the starting materials showed that rice and tapioca starch had a higher level of natural contamination than potato starch. All investigated starches met the requirements of the European Pharmacopeia for microbiological quality of solid oral dosage forms. α-Lactose monohydrate/potato starch tablets, inoculated with *Aspergillus niger* spores spoiled due to mould growth, when stored under extreme tropical conditions (31°C and 95% relative humidity). Under these conditions tablets prepared with α-lactose and rice or tapioca starch spoiled due to the growth of natural contaminants. No growth of bacterial cells (*Bacillus brevis*) was observed during storage under these conditions. When the tablets were stored under more moderate conditions (31°C and 75% relative humidity) they were not at risk to microbiological spoilage. The addition of preservatives (sodium methylhydroxybenzoate or potassium sorbate) was evaluated with respect to the efficacy against microbiological spoilage of tablets. A concentration of 1% w/w of either preservative prevented growth of *Aspergillus niger* on α-lactose/potato starch tablets, stored at extreme tropical conditions. Addition of a preservative to α-lactose/potato starch tablets contaminated with *Bacillus brevis* spores, did not affect the viability of these bacterial spores. The addition of preservatives to tablets prepared with α-lactose and rice or tapioca starch and stored under extreme tropical conditions, prevented microbiological spoilage caused by the growth of natural contaminants.

In the **Chapters 5 and 6** the influence of the tropical climate on the physical properties of tablets is investigated. In **Chapter 5** a factorial design is used to describe the influence of four adjustable variables on physical tablet properties (crushing strength and disintegration time) of α-lactose/rice starch tablets. The four adjustable variables were: two process variables (compression force and starch concentration) and two storage variables (temperature and relative humidity). Since the main parameter of interest is the decrease or increase in the physical tablet properties, the ratio of the parameters after storage to the initial parameters, was calculated for both the crushing strength and the disintegration time and used as dependent variable. The use of the Storage to Initial Ratio (SIR) for the different tablet parameters was evaluated and compared with the use of the absolute tablet parameters after storage. The Storage

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to Initial Ratio (SIR) for the different tablet parameters proved to be a suitable measure to express the physical stability of the tablets.
In **Chapter 6** the Storage to Initial Ratio (SIR) is used to select excipients which are least influenced by storage under tropical conditions and can be used in tablet formulations for tropical countries. Tablets were prepared from binary mixtures of a filler binder (α-lactose monohydrate, anhydrous ß-lactose or dicalciumphosphate dihydrate) and a disintegrant (corn, potato, rice, tapioca starch, sodium starch glycolate or crospovidone). A factorial design was used to study the influence of disintegrant concentration, storage temperature and relative humidity on the physical tablet properties of the tablets. α-Lactose monohydrate and anhydrous ß-lactose proved to be suitable filler binders for use in tablet formulations for tropical countries. The four starches and sodium starch glycolate, in combination with α-lactose can be used as a disintegrant.

In the last three chapters of this Thesis different tablet formulations are proposed for use in tropical countries. The physical and microbiological stability during storage under tropical consumers conditions of the proposed formulations is considered. With the selection of the excipients, attention is paid to the price and the availability. If possible, native excipients are selected, other excipients are available worldwide. Generally the preparation of tablets by direct compression is preferred, since it is a cheap method, consisting of only two process steps: mixing and compaction. However, sometimes the use of the wet granulation technique is necassary, when the drug does not have sufficient binding and/or flow properties. The proposed standard formulations are based on either the preparation of tablets by means of wet granulation (**Chapter 7**) or by direct compression (**Chapters 8 and 9**).
With the proposed formulations tablets were prepared to which model drugs were added. All selected model drugs are on the List of Essential Drugs of the WHO.
In **Chapter 7** standard granulations are proposed based on α-lactose monohydrate and rice or tapioca starch. Both granulations were used to prepare tablets with two model drugs (mebendazol, an anthelmintic or diazepam, a psychotherapeutic). Both formulations resulted in tablets with good initial tablet properties and sufficient physical and microbiological quality after storage under tropical conditions.
In **Chapter 8** standard tablet formulations for direct compression are proposed for the preparation of tablets by direct compression. The used filler binders were α-lactose monohydrate, anhydrous ß-lactose and modified rice starch. These formulations were evaluated by adding two model drugs (diazepam, a psychotherapeutic or hydrochlorthiazide, a diuretic). Both formulations resulted in tablets with sufficient properties, both initially as well as after storage under tropical conditions.
In **Chapter 9** modified rice starch is used as filler binder to prepare tablets. Modified rice starch is a filler binder with excellent flow properties and sufficient binding properties after mixing with a lubricant. Tablets were prepared with several model drugs (diazepam, a psychotherapeutic, hydrochlorthiazide, a diuretic or isoniazid, a

tuberculostatic). The properties of the prepared tablets met the USP XXI requirements.
In **Chapter 10** tablet formulations are recommended, which can be used in countries with a tropical climate.

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