In this study, the development of a system with a constant rate of drug delivery according to a novel release principle is described.

In chapter I the rationale for controlled release preparations is reviewed. In chronic medication, this type of dosage form prevails over the conventional tablets and capsules with fast drug release properties: the regular flow of drug from the controlled release products may provide an uniform therapeutic action over an extended period of time, without the occurrence of sub-therapeutic or toxic peak levels. Moreover, therapy may be improved by the increased patient-compliance, as a result of the more convenient dosage regimen and reduction of the side effects.

Not every drug is appropriate to be incorporated in controlled release preparations: less suitable are high dose drugs and drugs with a long half-life, with a local or irregular absorption in the gastro-intestinal tract or with a lack of blood level/activity relationship.

The gastric residence time is a factor of major importance for the bioavailability of controlled release products, when physiological factors of the digestive system like pH, enzymes, bile salts and motility of the alimentary canal affect the rate of drug delivery. For dosage forms which have the dimensions of tablets or capsules, the transit rate through the stomach is dependent on gastric emptying.

In discussing the various methods to control the release of drug by galenical means, oral controlled release products available in Holland are used as a reference. The dosage forms are classified as: 1) enteric coated preparations 2) repeat-action products 3) slow release particles in capsules and tablets 4) matrices of waxes and fats 5) matrices of polymers 6) ion exchange resins and 7) systems with drug release by osmosis.

Chapter II reports on a model for the principle of drug release from a system, developed in this study (the megaloporous system). Drug delivery from the system is considered to be the result of the interaction between two phases: 1) a continuous phase (housing phase) with slow penetration characteristics for the extraction liquids and 2) a phase (restraining phase) with properties of releasing drug over an extended period of time. Immersion of the system causes liquid penetration from all sides into the housing phase, comprising a large amount of soluble ingredients by the insoluble excipients in the leached skeleton of the granules. Liquid penetration into the insoluble ingredients by the insoluble excipients in the housing phase. The concentration of liquids in the large pores of the leached skeleton of the granules showed a decrease with time. From these experiments it demonstrates a large flexibility with respect to the constant release characteristics, altered. This flexibility with drugs with different water solubility and with respect to the constant release characteristics, altered.
amount of soluble ingredients. Dissolution of these ingredients provides very large pores in the system (see photograph on page 141; it shows a leached skeleton of the megaloporous system (diameter 13 mm), constituted by the insoluble ingredients of the restraining phase.

Liquid penetration into the inner parts of the device discloses an increasing part of the restraining phase surface area, available for drug delivery to the liquids in the pores. The rate, at which the drug releasing surface of the restraining phase is exposed to the extraction liquids in the large pores, decreases with respect to time, but simultaneously, the total pore surface area exposed to the liquids and contributing to the release process, increases. When the composition of both phases and the construction of the system are properly chosen, this process results in a constant rate of drug delivery from the device.

This modelistic approach of the delivery of drug from the megaloporous system provides an explanation for the experimental results.

Chapter III reports on the effects of composition and construction of the megaloporous system on the in vitro drug delivery. 

Drug release from the system appears to depend on the concentration of the insoluble excipients (carboxyvinyl polymer and magnesium stearate) in the housing phase. The concentration of the polymer can be varied from 0 to 15% without impeding the characteristic of constant drug delivery from the system. For a polymer concentration of 25%, the particular system shows non-linear release profiles.

The concentration of Eudragit® RS polymer (at least from 15 to 30%) in the restraining phase, the initial particle size of the composite granules, the volume fraction occupied by the restraining phase in the system, and the concentration of soluble excipients in the restraining phase could be changed without sacrificing the phenomenon of constant theophylline delivery from the megaloporous system. Only at high loadings with restraining phase material (about 75% of the volume), the system showed a decrease with time in the rate of drug release.

From these experiments it can be concluded, that the megaloporous system demonstrates a large flexibility in preserving constant theophylline release characteristics, when factors of composition and construction are altered. This flexibility is a favourable property, as it indicates that drugs with different water-solubilities may be incorporated successfully with respect to the constant release characteristics of the system.
In chapter IV, the release characteristics of theophylline from two formulations of the megaloporous system (preparations B and C) and from Theolin® retard (preparation A) in vitro as well as in vivo are evaluated. Preparation A was included as a reference, since it has demonstrated adequate controlled release properties in vivo. Approaching the ideal of constant drug delivery in vivo more closely than other commercially available theophylline products (Hendeles et al. (1984)). In vitro, preparation A demonstrates a biphasic drug release profile, which appears to be sensitive to the pH and the dissolution model. The extraction rates of theophylline in acidic conditions is constant, similar and independent of the dissolution model for both megaloporous systems. In buffered medium (pH 6.8), the rate of drug delivery from megaloporous preparation B is found to be lower in the paddle apparatus and for megaloporous preparation C faster in the modified disintegration tester, when compared to the rates in the respective dissolution models at pH 1.

The three dosage forms were evaluated in vivo with a neutral solution of theophylline as a reference. Preparation B released its theophylline content incompletely during the 32 h of plasma measurements, whereas no significant difference from complete absorption was found for either preparation A or preparation C.

To allow comparison of the in vivo release from oral controlled release dosage forms with the ideal performance (IP) in vivo, a value (the DIP) is introduced, which represents the quantitative deviation between the release from the dosage form and the ideal performance in vivo. Preparation A shows a similar DIP-value as megaloporous preparation C. The DIP-value for preparation B is found to be considerably higher, indicating that the release from this preparation in vivo deviates more from linearity.

The in vivo delivery of theophylline from preparation A and preparation C compared with the release of the drug from both preparations in vitro reveals, that the rate in the two dissolution models appears to be about 1.5 times faster than the rate for the preparations in vivo.

In chapter V, the theoretical basis of the drug release is analyzed for a system, which differs in composition and construction principle. The relationship of the drug containing particle release and the convolution integral is obtained. In general it can be concluded that spherical carriers compared to theophylline products from linearity that enhances particle.

When a second monodisperse particle is incorporated in one carrier, an approximately constant release rate is found. When the parameters affecting the release are properly chosen, the in vivo release of drug from the dosage form delivers about 80% of the DIP in vivo.

This theoretical study on the carriers, comprising "slipsticks" by a process of surface erosion as an interesting tool in the development of carriers characteristics.

Hendeles, L., Iafrate, F. Pharmacokinetic basis of theophylline products.
a system, which differs from the megaloporous system with respect to composition and construction. The same model for the drug delivery principle is applied, as appeared useful for the megaloporous system (Chapter II). The release of dissolved drug from these carriers of drug containing particles is calculated by mathematically solving a convolution integral.

In general it can be concluded that the release characteristics of spherical carriers comprising "slow-release" drug particles deviate less from linearity than the release profile of a spherical drug particle.

When a second monodisperse system of isometric drug particles is incorporated in one carrier, the release kinetics deviate even less from linearity.

An approximately constant rate of drug release is shown by a system of two carriers, each containing one monodisperse system of drug particles. When the parameters affecting drug delivery from this system are properly chosen, the initial deviation from linearity in the amount of drug released from one of the carriers is completely eliminated by the release of drug from the second carrier. This system of two carriers delivers about 80% of its drug content at a constant rate.

This theoretical study shows, that the application of a system of two carriers, comprising "slow-release" drug particles and releasing the drug by a process of surface erosion or dissolution, appears to be an interesting tool in the development of systems with constant drug delivery characteristics.