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Ph.D. Thesis

Quality Development of Semisolid Dermal Drug Delivery Systems

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Introduction

Semisolid dosage forms are coherent systems with a particular structure. Creams and hydrogels are preparations used widely in medicinal therapy and cosmetology. In my thesis parameters of great importance in the quality development and control of w/o creams and ambiphilic creams as well as of hydrogels were investigated from among the semisolid dosage forms with dermal application.

Today the factual knowledge published in literature concerning the properties of these material systems is almost confusingly immense and full of contradictions.

However, it seems that this extensive knowledge and experience is insufficient to optimise the formulation and stability of creams and hydrogels. Another important task in this field is to set the release kinetics of the incorporated drug. Some data and examination methods necessary for the selection of the components and for the determination of the optimum concentration are lacking. The components of the stability of these systems are not known and the extensive exploration of the factors determining drug release is still to be carried out. It is not accidental that no pharmacopoeia includes an official system of norms for qualification – based on the structure and deformability – of semisolid dosage forms. Manufacturers evaluate their products with their own norms, developed by themselves, thus the qualification system is characteristic not only of the product but of the manufacturer as well. The assessment of quality independently of the manufacturer demands uniform quality improvement and control in

investigating the structure of semisolid preparations, too. This would ensure, by optimising formulation, the selection of components and the formulation of a stable, attractive semisolid preparation with good applicability and the desired effect.

As regards the structure and drug release studies of creams and hydrogels in pharmaceutical technology, it can be stated that this field is undergoing a dynamic development. However, several detailed examinations are still to be performed before we can plan the composition of these dosage forms, set the parameters of production technology and determine the optimal values of their functional properties on due theoretical grounds.

Aims

The aim of my thesis was to investigate the effect exerted by important factors of dosage form development on structure in the case of semisolid drug preparations and more precisely w/o and ambiphilic creams and hydrogels, and also to study the interaction between drug release and microstructure. The focus of my research was given by the possibility that the formation of coherent systems and the changes of structure can be monitored successfully and characterised quantitatively with rheological measurements.

The following issues were to be studied:

- selection of the rheological characteristics of the greatest importance with respect to product development,

- exploration of factors influencing structure formation, studying the relationship between these factors and the rheological parameters, and if possible, to describe it with functions,
- description of the mechanical stability of the formed structure with rheological characteristics,
- studying the kinetics of drug release,
- elucidation of the relationships between drug release and consistency.

Results and discussion

The factors responsible for the structure formation of creams were analysed systematically. My aim was to achieve as high a water content in the creams as possible, on the one hand in order to perform an extensive study of structure formation, and on the other hand because a higher water content will result in more attractive appearance and better applicability for the user. This explains why the detailed investigation of the quantity of incorporated water and the factors influencing this was carried out.

The factors with decisive influence on the structure and stability of w/o emulsion creams were selected. A flow chart was made to facilitate the development and control of w/o emulsion creams. My major findings are going to be summarised in the following.

- The contact angle of wetting plays a significant role in the structure formation of w/o creams. In these systems the emulsifier, or a great part of it, is found on the boundary surface of the oil and water phases. The calculation of the contact angle of wetting and the associated properties were studied in great detail. The increase in the concentration of the

emulsifier results in the considerable decrease of the contact angle of wetting but only up to a given value, over which the further increase in the surfactant concentration leads only to a slight decrease.

- Both the amount of the inner phase, which can be incorporated, and the water-retaining capacity of the already formed structure increase with the decrease of the contact angle of wetting. A linear regression was found to exist between these two parameters. The determination of the contact angle of wetting of the water-free base containing the emulsifier in different concentrations before the incorporation of the inner phase is essential in the improvement of w/o creams.
- An exponential relationship was found to exist between the contact angle of wetting of the water-oil phase and the droplet size of the inner phase of the emulsion cream.
- The great number of the examined w/o emulsion creams containing mixed emulsifiers and self-emulsifying bases all were, irrespective of the water content, thixotropic systems with a yield value. The rheological parameters tended to increase with the water content. Thixotropy and structural viscosity characteristically increased with water content for both series. The greater the quantity of water emulsified in the inner phase, the higher the parameters characterising consistency will be.
- Viscosity and shear time functions can help to analyse the processibility and material transport of the creams. The small extent of initial structure break observed in the creams, which is not followed by significant viscosity decrease, ensures good processibility.

- The changes occurring in the microstructure of creams during storage can be monitored with the time depending rheological parameters.
- The value of the activation energy got during the investigation of the heat stability of creams provides a possibility for rapid numerical comparison or evaluation.
- The solidification characteristics of the gel structure formed from the melt constitute an essential question as concerns the optimal production technology. The equation describing the temperature-time dependence obtained by measuring the temperature during the mixing of the melted mass was found to be suitable for determining this parameter. The slope of the line obtained in this manner is the cooling rate value of the creams.
- Creams containing water in the inner phase also exhibit considerable evaporation loss. The mass decrease of creams is in a linear relationship with the increase of the mass percentage of the inner phase as the function of the square root of time. The evaporation rate calculated from these linearized functions increased considerably with the increase of the emulsified water content.
- A power function relationship was found between the structural viscosity of creams and the shear rate gradient.
- A relationship was found between the droplet size of the inner phase and the quantity of the drug released. The increase in the size of the emulsified droplets resulted in increasing the quantity of the drug released.
- The increase of the mass ratio of the inner phase increased the quantity and rate of drug release.

- In the case of ambiphilic creams, the quantity of the released drug was increased by the quantitative increase of the aqueous phase and decreased by the quantitative increase of the oil phase.

Experiments were performed with a large number of hydrogels, during which the state of the hydrogel matrixes built up from polymers was examined and the relationship between the viscosity of hydrogels and drug release was studied.

- The hydrogels of the studied polymers, with the exception of Avicel RC 591 the bulk of which has a microcrystalline structure, did not show thixotropic behaviour.
- The concept of the structure formation constant was introduced for the description of the hardening of the structure. In the examined polymer matrix series an exponential relationship was found between the viscosity of hydrogels and the concentration of the polymer. The constant of these equations expresses the hardening of the structure, it gives a quantitative description to what extent the volume of the pores decreases and their winding increases with concentration. This constant is going to be called structure formation constant hereafter.
- The hydrogels in our study were viscoelastic systems. The changes in the plastic and elastic state of the gels can be monitored with the examination of the concentration dependence of the loss and storage moduli.
- The interaction resulting between the polymer matrix and the incorporated drug was pointed out with the analysis of flow curves.

- A power function relationship can describe the decrease in drug release taking place upon the effect of increasing the concentration of the polymer.
- The concept of drug release constant was introduced for the description of the drug release decrease occurring with the increase of the polymer concentration in the matrixes built up from various polymers. The absolute value of this constant expresses to what extent drug release decreases. Henceforth this constant is going to be called drug release constant.
- Based on our investigations performed with polymers it can be stated that during the formulation of hydrogel-based semisolid preparations the structure formation constant and the drug release constant should be determined and used for the selection of the hydrogel best suited for the given therapeutic aim and for the given drug.

Publications related to the subject of thesis

Papers:

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