10 Summary

Within the scope of this dissertation the production of so called „compounds“ for direct compression as well as the production and characterisation of the drug and polymer dispersions included in these compounds are described. The principle of the compounds was to take advantage of the nanoparticulate drug and a polymer controlling the release by combining them in a powder for direct compression for oral drug delivery. The production of the compounds was supposed to be a simple combination of high pressure homogenisation and spray drying to facilitate a low cost and easy industrial production of larger batches.

In the first step the production of the nanosuspensions was examined with different model drugs. Nifedipine was chosen as a crystalline substance with a low half-life for oral therapy, charcoal as an amorphous substance of potential diagnostic importance and azodicarbonamide (ADA) as an example of a low soluble and instable active agent.

The attention was mainly turned to the following four points:

1. the stability of the developed formulations
2. the determination of the maximum concentration of the drug in the dispersion
3. the connection between homogenisation pressure and particle size
4. the suitability of the dispersions for spray drying.

It was also the question if and how the physical properties (crystalline / amorphous) have influence on the results of homogenisation.

Concerning stability a formulation could be found by optimising the surfactants in an extensive screening for each drug that guaranteed the possibility of further processing in a suitable time frame. Especially the developed nifedipine nanosuspension (10 %) could be stabilised for up to 36 months with only negligible particle growth if stored under 25°C. It should be stated, however, that a stabilisation over several months without aggregation and / or particle growth was not possible in every case, witch is a severe disadvantage of many nanoparticulate dispersions. For this reason it is especially important to develop dry final formulations by easy further processing.

So far a maximum of 10 % drug for the production of aqueous nanoparticle dispersions is described in literature. It was therefore the scope of this work to examine how a further increase of the concentration will influence the particle size. It was indeed possible to realise the production of dispersions with 30 % nifedipine. The resulting particle size after 20 homogenisation cycles at 1500 bar was only slightly higher compared to a 10 % suspension. The highly concentrated suspensions were stable over 28 days at room temperature. Concerning the labile drug ADA it had to be considered that a high energy input during homogenisation of a highly concen-

trated dispersion leads to the destruction of the molecule under formation of gas so the efficiency of particle destruction was reduced. Up to a concentration of 20 %, however, the suspension was formed in acceptable quality by only using a steric stabiliser.
The standard pressure for the production of nanosuspensions with high pressure homogenisation is usually 1500 bar applying 10 to 20 cycles. In the scope of this work it could be clarified, however, that nifedipine suspensions could be formed at lower pressures (e.g. 10 cycles at 150 bar) that had a mean particle size in the range of 1 µm. Even if the resulting dispersions should not be defined as true nanosuspensions anymore, this way of production could be identified as being a suitable alternative for sensitive substances. It was also found out that the efficiency of size reduction has a maximum at a certain drug concentration and decreases again afterwards, because the great number of particles reduces the effective forces in the homogenisation gap.
It was moreover possible to spray dry a 10 % nifedipine nanosuspension and gain a dry powder. The following redispersion could be performed without any problems and the resulting suspensions showed the same particle size as the original. Nifedipine was therefore chosen as the best candidate for the production of compounds.
Starting this research work the question was discussed if a solid drug crystal can be destroyed more easily by cavitation and collision forces than an amorphous and therefore disordered powder or vice versa. The tests with charcoal in comparison to ADA or nifedipine showed, that at least in this case an amorphous structure was a disadvantage. Although the resulting charcoal dispersions seem to be suitable for diagnostic purposes using ESR-measurements the mean particle size could not be reduced to the nanometer range even at low concentrations.

The second part of this work focussed on the topic of producing aqueous polymer dispersions (SPN = Solid Polmer Nanoparticles) by high pressure homogenisation, which could later be used as retarding component in the final formulation, i.e. the compound. For comparison commercially available dispersions like Aquacoat® were used.
Shellac and ethyl cellulose were chosen as model polymers. The questions were posed analogous to the ones for drug nanosuspensions: physical stability, the maximum concentration of polymer in the dispersion and the influence of production parameters on the particle size were examined. Because of the differing physical attributes of polymers, however, special attention was focussed on the parameter production temperature.
In conclusion of the results for ethyl cellulose the following can be stated: After an intensive formulation screening it was possible to develop a polymer dispersion

which is suitable for further processing in compound production (concerning stability and particle size). As crucial process parameters for the optimal reduction of particle size, the homogenisation pressure, the number of cycles and the selection of suitable stabilisers were identified. The mean particle diameter of the dispersion could nevertheless not be lowered to less than 1.5 µm after 20 cycles, a further reduction to the range of commercial dispersions (approx. 170 nm for Aquacoat®) was not possible at lab scale.

Processing the polymer at conditions above the glass transition temperature, as described by Müller and Specht, and also homogenising slightly above the freezing point did not show any advantages. Concerning long-time stability it was not possible to optimise the formulation and / or production process in a way that inhibited sedimentation and caking of the particles. As the increase of the cycle number led to a steady decrease of particle size it can be postulated that a further destruction of the particles could be realized in the continuous modus of larger homogenisers.

Additionally aqueous ethyl cellulose dispersions could be produced for the first time with a polymer concentration of 25 % showing a particle size in the lower micrometer range. These suspensions were much more stable due to their higher viscosity, storing these concentrates for a longer time seems feasible.

Concerning shellac, further results could be obtained considering the basic research already described by Specht in regard to the manufacturing process. By optimising the process parameters the resulting particle size could reproducibly be reduced to the nanometer range. The diameter of the main population (D 50 %) was 520 nm and the D 99 % about one micrometer. The mean particle diameter determined with photon correlation spectroscopy was 368 nm showing a polydispersity index of 0.135. By adding surfactants to the dispersions the problem of caking could be reduced in a way that the formulations were stable for at least three months.

In the final part of this dissertation, compounds - at first drug-free - were produced and tested for their particle size, character and flowability. The polymers were used in the form of the aqueous dispersions (commercial and own production), as a further excipient lactose was chosen, varying the relation of lactose and polymer in a wide range. The resulting particles always showed a spherical shape and a continuous outer lactose layer, which is highly desirable for direct compression of the powder. They varied concerning their particle size and surface roughness, however, depending on the kind of polymer and its mass fraction. Using Aquacoat® the fraction of polymer in the particle could be increased up to 80 %. Whereas low polymer fractions led to the formation of polymer bridges between the compound particles, this could not be observed at percentages higher than 30 %. The particle size measured with laser diffraction decreased therefore with increasing polymer fraction from approx. 21 µm to 8 µm. At high polymer concentrations slight circular elevations of the parti-

cle surface could be detected by REM which were identified as being the polymer particles due to their size. Compounds could also be produced using the much bigger “self made” ethyl cellulose dispersions but they showed a much rougher surface characteristic.

The flowability of the different compounds was defined by the flow angle and could be adjusted by adding low amounts of Aerosil 200 to reach values suitable for direct compression of the powder.

Finally the different active agents, especially nifedipine, were integrated into the compound particles using the aqueous dispersions prepared by high pressure homogenisation. It could be shown that the drug crystals were completely included in the lactose matrix. The flowability of these compound formulations was also comparable to the one of placebo formulations.

As a final result the developed compounds contained all relevant ingredients of the desired peroral formulations (e.g. matrix tablets). Separation of the different components during the tabletting process is therefore not possible. The drug nanoparticles could be preserved during the compound production. For two of the examined drugs a similar particle size distribution could be measured after redispersion of the powder compared to the original nanodispersion so that the advantages of the nanoparticles are still valid.

The compounds developed in the frame of this research work can therefore be seen as an innovative particulate system for the easy production of oral controlled release dosage forms.

Their production is performed without using organic solvents by only applying the standard technologies high pressure homogenisation and spray drying. The compression of tablets from these compounds and their dissolution profiles are currently under investigation on the basis of this work in the research group of Prof. Müller.