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Ph. D. Thesis

Optimization of process parameters of coated pellet production

by

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1. Introduction

In case of classical dosage form the active pharmaceutical ingredient (API) incorporated in the preparation has an immediate effect. But in case of several diseases' treatment (e.g. asthma, allergy, diabetes etc.) a constant concentration of API is needed in the plasma. Sustained effect can be reached in several ways: by using chemical, physiological and technological methods that can be applied together as well.

Solid dosage forms (pellets, tablets or capsules) are the most frequently used medicines (about 80%) in therapy. In the course of the production of solid dosage forms numerous problems have to be taken into consideration. There is a wide range of methods for assuring sustained release, for example by choosing the appropriate vehicle, forming inclusion complexes, using microcapsules or by applying suitable coating material. Film coating is one of the most widely used methods during the preparation of solid dosage forms therefore it is of great theoretical importance.

The elimination of unfavourable phenomena and problem solving are highlighted fields in pharmaceutical technology. For an understanding of these processes, a deep investigation of the interactions between the applied materials and equipment, and the effect of the parameters of the production method is necessary. During the work the approach of "Quality by Design" was followed, for this reason factorial design was used. The definition of critical control points during the formulation is important to reach the suitable quality.

2. Aims

The two main parts of this study were to investigate the production of coating liquids containing insoluble components and to develop matrix formulation for pellets made by extrusion/spheronization containing the same insoluble particles. The main aim was to define the critical point of both processes.

The primary objective was to establish parameters that can be applied for the mixing of aqueous dispersions and pigment suspensions. These parameters are not known in the literature, and in general the settings are empirical. Free films were also prepared and investigated by different physicochemical methods.

The second aim was to develop laboratory-scale I. (LI.) and laboratory-scale II. (LII.) suitable matrix formulation for pellets made by extrusion/spheronization using different types of

apparatuses. The physicochemical parameters and the dissolution profiles of the products were compared. Finally, the pellets were coated by using coating liquids with and without API.

3. Section I.

The aims of this chapter were firstly to investigate the suitability of an energy-dispersive X-ray fluorescence analyser for rapid measurement of the sedimentation of titanium dioxide in aqueous suspensions and secondly to establish parameters that can be applied for the mixing of pigment suspension and polymer dispersion. The homogeneity of the liquid prepared and dimensions of the vortex cone formed were evaluated.

Commercial titanium dioxide was dispersed in distilled water at a concentration of 10%. The fluid was stirred with an Ultra-Turrax mixer. A 2^3 full factorial design was applied for different mixings; the factors were the stirring rate (X1), the stirring time (X2) and the volume (X3) (Table 1.).

Table 1: Experimental design

Sample	X1 (rpm)	X2 (min)	X3 (ml)
S1 (---)	9500	5	100
S2 (+--)	17500	5	100
S3 (-+-)	9500	10	100
S4 (++-)	17500	10	100
S5 (--+)	9500	5	200
S6 (+-+)	17500	5	200
S7 (-++)	9500	10	200
S8 (+++)	17500	10	200
S9 (000)	13500	7,5	150

The titanium contents of the pigment suspensions and the enrichment of the pigment at the bottom of the sample holder were measured with an energy-dispersive X-ray fluorescence analyser. The sedimentation profile showed no fundamental differences between the characteristics of the sedimentation curves (Figure 1.). However, when comparing the sedimentation times by means of the factorial design, significant effect of the stirring rate, the time and interaction of these factors was revealed. The higher are the values of these factors, the longer is the sedimentation time.
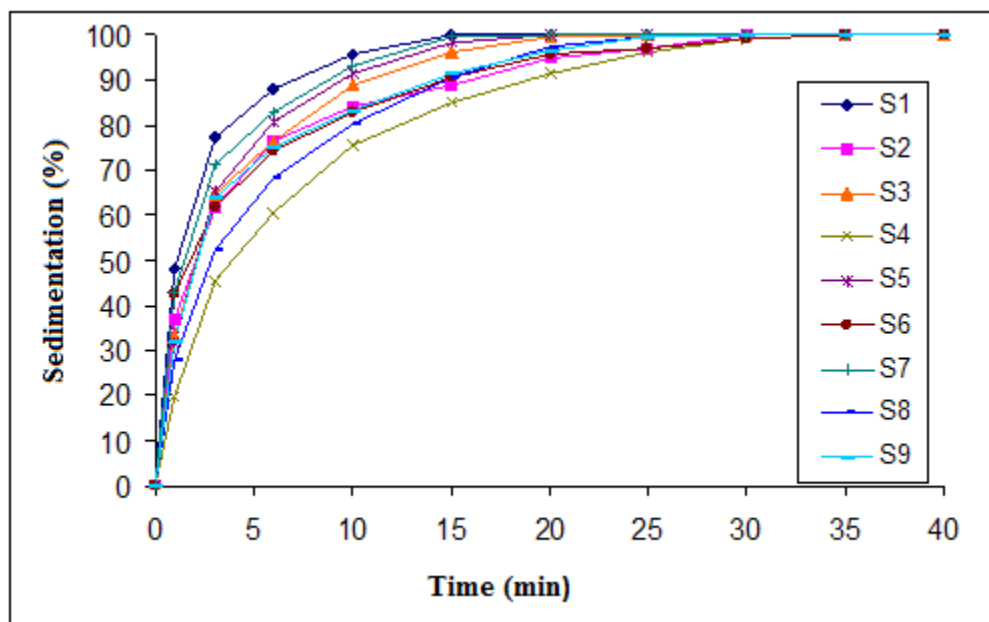
Figure 1. Sedimentation curves for pigment suspensions

For the **determination of homogeneity** the coating suspension was prepared according to our previous results. Eudragit$^®$ NE 30D was applied as a polymer dispersion, which contains 28.5-31.5% dry matter (poly (ethyl acrylate, methyl methacrylate) 2:1) and approximately 1.5% Nonoxynol 100 as emulsifier. It is insoluble in water, displays low permeability and pH-independent swelling, and is highly flexible. It is an aqueous dispersion that is highly suitable for sustained-release film coatings and for sustained release granules. The composition of the liquids was as follows: 20% pigment suspension, 30% polymer dispersion and 50% purified water. A 2^4 full factorial design was applied to optimize the mixing of the polymer dispersion and the pigment suspension; the factors included were the quantity, the stirring time, the motor stirring speed and the stirrer size.

The solid content at the bottom of the sample holder was determined by a gravimetric method. The liquids and the dried samples were weighed with an analytical balance. The concentration of the polymer dispersion was 30.067±0.015%, i.e. the concentration of the prepared liquid was 17.033%. The deviation of the solid content from the average measured concentration of the solid was calculated. The most important parameter was the stirring speed. Increase of this parameter decreased the variance. The other factors alone were not significant (least of all was time), but there were three significant two-factor and three significant three-factor interactions.

Because of the large number of parameters, an exact mathematical description of the motion of the liquid is very difficult. For this purpose we chose to assess the volume of the vortex, as it can be easily determined during homogenization. A 2^3 full factorial design with a central point was used to determine the factors affecting the **volume of the mixing whirlpool** (Figure 2). The factors were the quantity, the stirring speed and the stirrer size. The volumes were calculated by measuring the height of the liquid during homogenization and without the mixing with callipers having an accuracy of 0.02 mm.
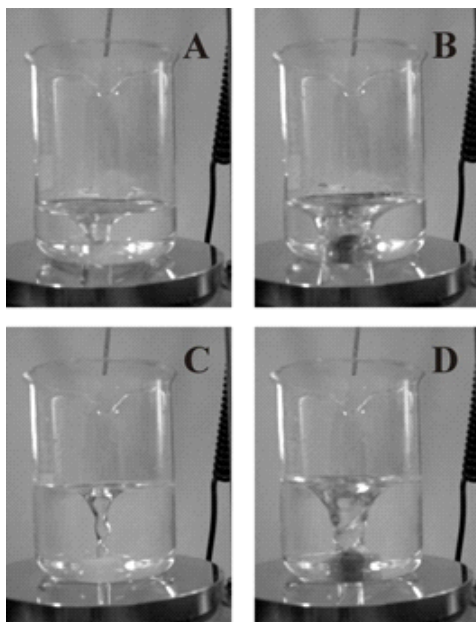

Figure 2: Comparison of the vortex cone during the stirring of water

The results showed that the vortex volume varied considerably (0.335 – 6.527 cm^3) with the different set-ups. The effects of the factors also differed greatly. The highest value was detected for the mixing speed. The factors and their interactions were not significant.

Evaporation of a similar composition containing a volatile component (ethanol) was also studied where the effect of an antifoaming agent (Dimethicon) was measured. The effects of different operational factors were compared by means of factorial designs.

The presence of ethanol in the liquid changed not only the extents of the effects of the factors, but also their relative importance as concerns the evaporation process. The highest difference in effect of a given factor was detected for the stirring rate, while the lowest difference was observed for the duration of stirring. A high concentration of Dimethicon (6%) decreased the extent of evaporation, but not significantly.

In conclusion, our results revealed that the homogeneous distribution of the insoluble particles during mixing is more dependent on the factors affecting intensiveness of moving than the mixing time. Different factors must be considered to describe this motion, e.g. the speed of the particles and the liquid, the size of the particles, their sedimentation rate, the lifting forces, the viscosity of the liquid, the size and shape of the stirrer and the container etc. Overall, it can be stated that every individual factor influenced the motion of the particles during the mixing, but the resultant of the effects of the different factor was more important as concerns the interactions.

In the study of evaporation it could be stated that Dimethicon does not result in a relevant change in the evaporation in these systems containing ethanol as a volatile component. Accordingly, primarily the operational parameters must be considered during the formulation of these compositions. Hence, determination of the critical points of coatings with a liquid containing a volatile component cannot be avoided because the vapour of such materials can be very dangerous.

4. Section II.

The aim of this part was to investigate the structure of free films of Eudragit® L 30D-55 containing different concentrations of diclofenac sodium by conventional physicochemical methods and positron annihilation spectroscopy.

Eudragit® L 30D-55 is an aqueous dispersion of anionic polymers with methacrylic acid functional groups. The coating liquid compositions contained **titanium dioxide, talc, triethylcitrate, dimethicon** as antifoaming agent, and microcrystalline **diclofenac sodium** in different proportions as API. The pigment suspension containing 0%, 1% or 5% of the API was prepared, then it was poured into the polymer dispersion and mixed with an overhead stirrer. As a final step, the mixture was sieved.

The ready coating liquid was tested with an **MFFT** apparatus. Our results showed that the MFFT of these films was 24 °C, which corresponds to the value given in the Eudragit brochure. This means that the components had no effect on the MFFT of the bulk film.

The free films were prepared by pouring the mixture onto a Teflon surface, and drying it. The apparatus and the software for the **deformation tests** were developed in our department. The mechanical strength and the deformation of the free films can be described by deformation curves. These curves showed that these free films first undergo a viscoelastic deformation, which

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is followed by an elastic section, at the end of which breaking occurs (Figure 3). Together with the increase in the content of the API, the strength of the films decreased considerably. By increasing the concentration of API, more insoluble particles will be incorporated in the structure of the polymer matrix. This will cause the given changes in the physical parameters.
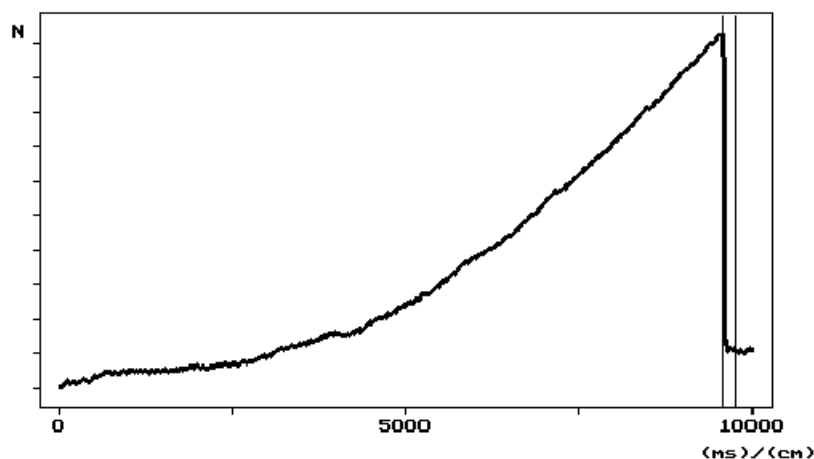

Figure 3: Deformation curve of free film containing no active pharmaceutical ingredient (Film1)

The **surface roughness** of the free film (Film1) atomized on a glass surface was examined. The arithmetic mean deviation (Ra) was 4.21 ± 0.98 μm, root-mean-square deviation (Rq) was 5.47 ± 1.46 μm, and maximum height of the profile (Rz) was 28.24 ± 6.52 μm. These results show the importance of the pretreatment of pigments.

Free films were tested with an OCA 20 optical **contact angle**-measuring instrument. The drop profiles were fitted with the Wu model included in the DataPhysics software. The Wu equation was used for the calculation of surface free energy (SE). If the SEs of the solid materials are known, the spreading coefficient (S) may be computed and the interactions between the film layer and the API may be predicted. It can be concluded that the content of API influenced the SEs of the free films. On the increase of the amount of the API, SE, the polar part of SE, the polarity and the work of adhesion (W_a) increased but the spreading coefficient (S_{12}) decreased. The higher polarity and the work of adhesion indicated the better sticking of the film on the surface of the hydrophilic core. The positive value of S_{12} demonstrated that the film will spread on the surface of the API, and the crystals of the API can be incorporated into the polymer film.

Samples of the cast films obtained and the API were used for **differential scanning calorimetry** (DSC) analysis and **thermogravimetric** (TG) analyses of the API were also

performed (Figure 4). The samples were heated to 300 °C (10 °C/min) then cooled to 25 °C and heated again with the same parameters. In the initial section, a glass transition can be seen for all the films. In the third section (the reheating phase), a glass transition was detected for API content of 0% and 1%. The material with an API content of 5% exhibited no glass transition. The reason may be that the API crystals disturb the internal structure of the film, leading to rearrangement of the macromolecules.
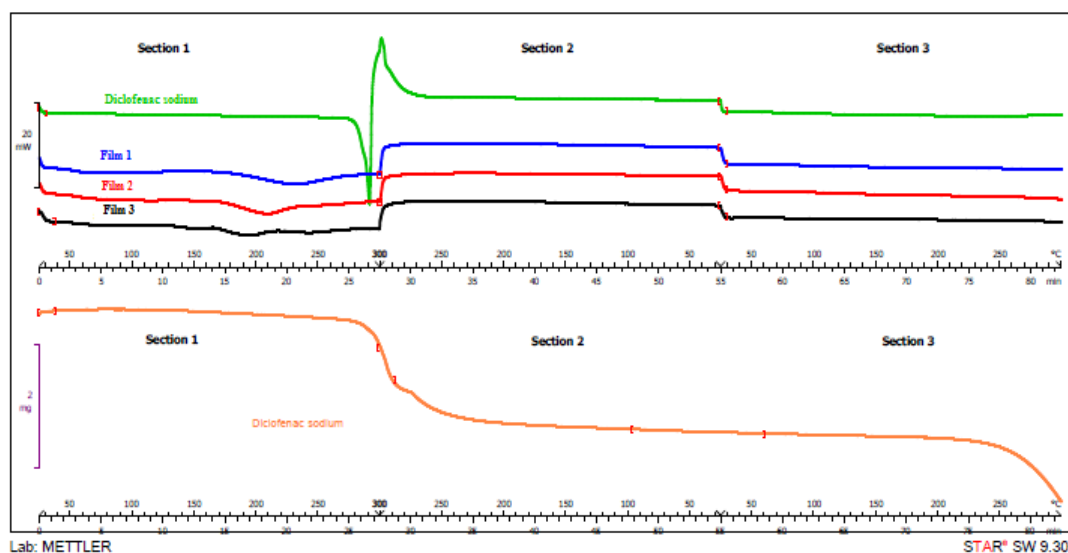

Figure 4: Differential scanning calorimetry and thermogravimetric curves.

The films were also tested by **positron annihilation lifetime spectroscopy** (PALS) after various storage periods. This measurement is very useful in the test of inner structure of polymers. It can be seen in Figure 5 that the o-Ps lifetime is decreased by the presence of API in the films.
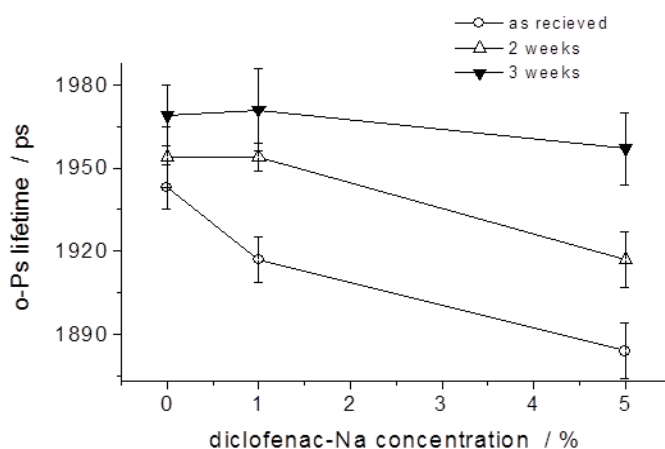

Figure 5: o-Ps lifetimes in films containing different amount of the API.

This decrease is not a consequence of a positron – diclofenac reaction because it disappears in the course of storage. It is most likely that, during the film formation, diclofenac occupies sites between Eudragit chains and, thus, distorts the original structure. The distortion leads to the formation of smaller free volume holes. During the storage period, the film absorbs water molecules from the air. The plasticizing effect of water helps the distorted structure to relax and, after three weeks of storage, all the films have a very similar structure. The average size of free volume holes is around 4.48 Å in every case. The o-Ps lifetime data suggested that the films containing the API are formed in a metastable structure.

As more and more API is added to the film, the original free volume structure of the polymer was gradually destroyed and free-volume holes became smaller. However, the distortion was not permanent. While the Film 1 (0% API) does not change significantly during a 3-week storage period, those containing the API did change significantly. After 3 weeks of storage, the average o-Ps lifetime indicated that these former effects of the API became negligible. The lifetime becomes independent from the amount of the API.

5. Section III.

The first aim was producing monolitical matrix pellets containing Eudragit® NE 30D by extrusion-spheronization, where the critical control points of the process were detected by means of a factorial design. Secondly the focus was to develop laboratory-scale I. (LI) and laboratory-scale II. (LII) suitable matrix formulation for pellets using different types of apparatuses. Last but not least the pellets were coated by coating liquids with and without containing API. In the composition of the pellets, **microcrystalline diclofenac sodium** was used as an active pharmaceutical ingredient (API), **microcrystalline cellulose** (MCC) and ethyl acrylate-methyl methacrylate copolymer (**Eudragit® NE 30D**) as binder and matrix-forming agents, and **purified water** as granulation liquid.

Part 1.

The solid components of the powder mixtures were homogenized with a Turbula mixer. First Eudragit® NE 30D and then purified water was added to the mixture in a high-shear granulator. The wet mass obtained was extruded by a mini screw and then spheronized. The pellets were dried under the same conditions. A 2^4 full factorial design was applied to optimize

the process parameters and the best composition; the factors included were the quantity of purified water, the liquid dosing speed, the speed of spheronization and the duration of spheronization

The particle size and the shape of the pellet surface were studied with a stereomicroscope. The **aspect ratio** was utilized for the evaluation of the shape of the particles. Samples prepared at a higher dosing speed required less spheronization time to achieve an acceptable aspect ratio, whereas the samples prepared at a low feeding rate could not be rounded during the given period of time. The negative coefficients indicate that increase of the dosing speed and the duration of spheronization results in a considerable decrease in the aspect ratio of the pellets.

The **breaking hardness** was tested for pellets (Figure 6). The strength tester and the software were developed in our institute (same as used by films but different specimen holder and stamp). The evaluation of the mechanical properties involved not only determination of the breaking hardness, but also investigation of the process of pellet deformation via study of the deformation curve.
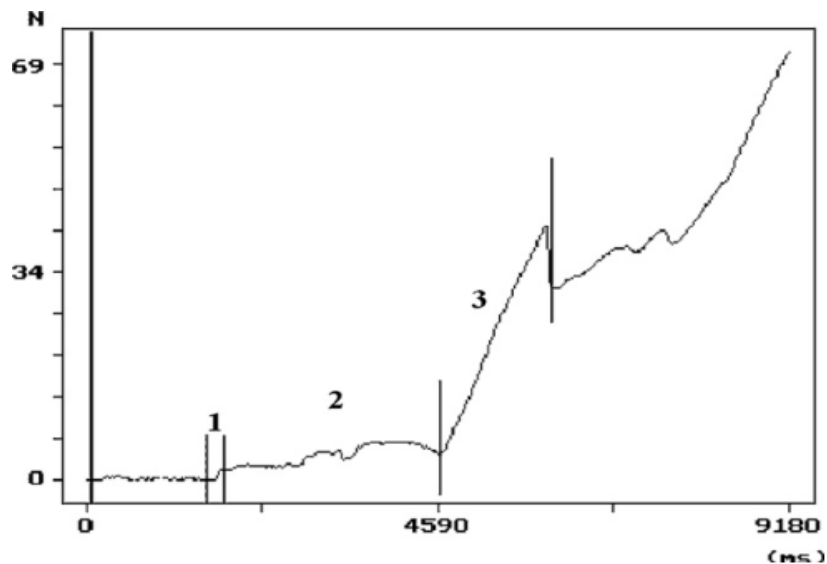

Figure 6: Curve of pellet deformation

The results suggested that the wetting rate of the extruded mixture has the greatest effect on the mechanical properties of the pellets. The negative value of the coefficient indicated that increase of the water quantity decreases the pellet hardness. This phenomenon is strongly connected with the dosing speed of the liquid, as revealed by the statistically significant value of the interaction of the two factors.

Nevertheless, while the physical properties of pellets seems to be optimized, a further optimization of the production process is necessary, since the large aggregates, which are forming during the aggregation results an elevated impeller torque, which causes an extreme demand of the apparatus. The aim of the optimization process was to avoid the apparatus from the demand and keep the aspect ratio of the pellets. While the most important influencing factor of this property is the dosing speed its value was increased to +2 level, while the water quantity was kept in -1. On the basis of these considerations a new combination of factors was applied, where we achieved matrix pellets with optimized characteristics (Figure 7).
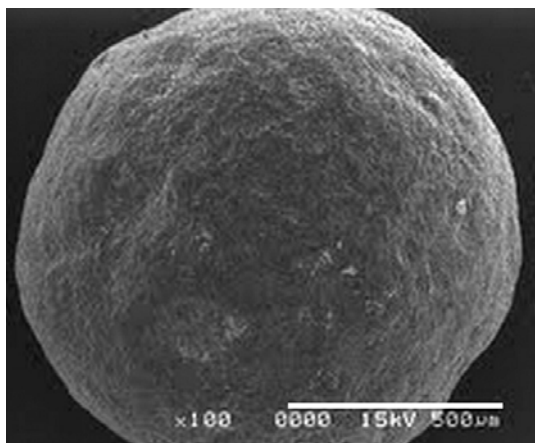

Figure 7: Surface of pellet with optimized characterictics (SEM)

The physical parameters indicated that this sample was suitable for **dissolution studies**. The dissolution medium consisted of phosphate buffer (pH 6.8), kept at 37.0 ± 0.5 °C for 4 hours. Absorbance was measured spectrophotometrically. The results showed that 50% of the API had dissolved after 40 minutes, and about 85% after 240 minutes. The dissolution curve was of saturation type, following first-order kinetics.

It was concluded that Eudragit[®] NE 30D can be used well as a binder and matrix former in pellets containing diclofenac sodium and produced by extrusion–spheronization. Through use of the factorial design, the process was optimized. In the case of the breaking hardness, the quantity of water and the dosing speed were significant factors, while in the case of the aspect ratio, the dosing speed and the duration of spheronization were significant. This information is indispensable for a more accurate knowledge of the preparation of the pellets and for detection of the critical control point of its development. On the basis of these results, a new sample was prepared that can be defined as optimized pellets. Dissolution studies revealed first-order kinetics

in the phosphate buffer. This means that this product may be used as a delayed release dosage form.

Part 2.

Composition was the same as for LI. but with the increasing of batch size the quantity of purified water was necessary to increase to reach the suitable wet mass. But the ratio of powder and fluid was almost the same (1.015:1.065). The blended dry powders were wetted first with Eudragit® NE 30D dispersion and after that with purified water using a high shear mixer. The wetted mass was supplied to a flat die press and extruded through a flat screen with dies of 1 mm in diameter. Collected extrudate batches were spheronized and dried.

These pellets were studied **morphologically** and **mechanically** by the methods described in Part 1. Aspect ratio is quite the same in both, but the size became smaller in case of LII. Breaking hardness of both batches was high enough for further processing, e.g. coating. But there is a difference in the breaking hardness due to the use of different type of extruders and due to different size distribution. Different forces predominate during the two types of extrusion in the materials. Tensile strength of pellets was also determined, the results show that in this case the size of pellets is crucial.

Dissolution tests (Figure 8) were also carried out under the same circumstances as by LI. In all cases, the pellets show a matrix type of release because of the missing disintegration caused by the presence of MCC and Eudragit® NE. The results of dissolution studies shows that the dissolution rate of the LII-samples is the half of the original. This phenomenon probably can be due to the different texture of pellets resulted by the different power impulses and related deformations in the different extruders.
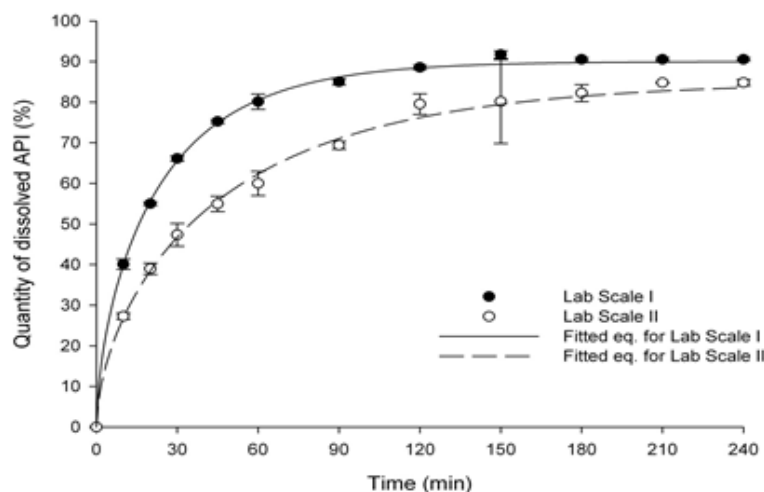
Figure 8: Dissolution of pellets

It can be concluded that this process could be accomplished by the use of a different apparatus, although the size of the pellets was smaller, the aspect ratios were identical. Breaking hardness of pellets was different but it was adequate. The difference can be explained by the use of different apparatuses and by the different size of pellets. Tensile strength data show that the textures of the pellets are different. In case of LI it is more compact than of LII. Dissolution tests showed similarities in the course of the curves but there was a significant change in the speed of dissolution in case of LII: dissolution rate was smaller and there was a bigger SD. It can refer to the fact that the use of flat dry press caused changes in the optimised matrix system that should be investigated more precisely.

Finally, in this case the operation of the two types of the extruders was different, although it can be stated that the similarity of the mixing parameters is assured. The difference of dissolution data can be explained by the difference of breaking hardness of the pellets. Although we had to change the composition to a certain extent, the process was basically simple. Quality of the products was not the same but it was adequate.

Part 3.

Matrix pellets produced in Section III./1-2. were coated in a Strea-1 fluid bed Wurster chamber. Coating fluids containing 0 and 4.375% of API (**diclofenac sodium**) were prepared as described in Section II. The coating liquids contained **Eudragit® L 30D** as a polymer that forms a enterosolvent film on the surface of the pellets. As a last step the coated pellets were dried.

Coating 2 was used only in case of LII. because the aim was to accelerate the starting rate of dissolution.

Dissolution studies were carried out according to the Ph. Eur. standards with a rotating basket. Dissolution curves of both pellets coated by Coating 1 are similar, after about 150 minutes the whole amount of API was dissolved. Dissolution of LII. pellets coated by Coating1 and 2 was also compared (Figure 9). The rate of dissolution by Coating2 was higher because after 20 minutes almost 50% of API was dissolved (It was about 35% in case of Coating1). This can be explained by the fact that the diffusion of API directly from the film layer occurs faster.
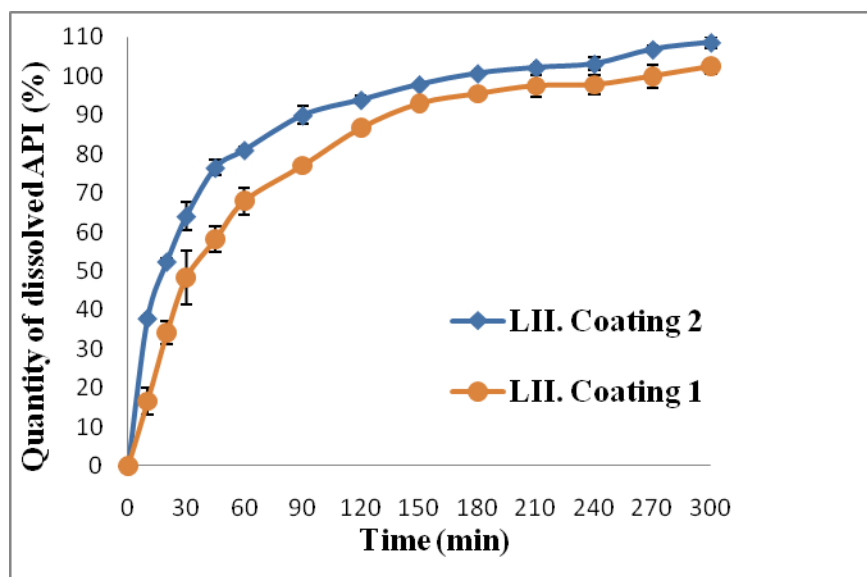

Fig. 9: Dissolution of LII. pellets coated by Coating1 and 2

It can be concluded, that the use of microcrystalline API in this coating liquid composition in this coating process is possible and the incorporation of certain amount of API in the coating layer accelerates the starting rate of dissolution. After this the matrix system ensured the sustaining dose for the proper time. Although the concentration of API in the liquid is limited (4.375%), this amount in the coating layer is sufficient for influencing the dissolution of API from matrix pellets. Based on the results, a faster dissolution can be achieved because the diffusion of API directly from the film is faster.

6   FINAL CONCLUSION, NOVELTY, PRACTICAL USEFULNESS

•   The preparation of a complex coating suspension was examined. An exact knowledge of the effects of technological parameters used during the formulation of a liquid containing a

pigment suspension is very important with a view to increase the processibility of insoluble particles in a coating liquid. It offers important information for manufacturing and assuring a proper coating layer.

• Because of the complex relationships of factors, it is very difficult to describe the optimum motion of the liquid. It can be stated, that changes in the dimension of the vortex cone can be informative during the mixing, but homogeneity testing must be performed previously because there is no obvious relationship between these parameters. The homogeneity of the liquid cannot be predicted directly from the features of whirlpool formation. Study of the connection of influencing factors and modification of the vortex cone is important for determination of the optimum operational parameters.

• Coating liquids always contain different additives that can influence the physical-chemical characteristics of the film formed. The presence of diclofenac sodium (or other API) changed the characteristics of polymer free films. This change could be confirmed by different physical-chemical methods.

• The use of MCC is indispensable for the extrusion-spheronization process. Based on the experiments it can be stated that MCC combined with Eudragit® NE 30D in correct ratio and quantity is suitable for the formulation of monolithic matrix pellets. These additives further the dissolution of API by diffusion. The results can give useful information and data for dosage form developers.

• In case of modified drug release systems API can be incorporated in the coating layer too for assuring this dissolution profile. API can modify the structure of the film formed which can influence the drug release.

Results experienced during this work can be used for the production of similar systems.

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