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Optimization of process parameters of coated pellet production

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CONTENTS

1. INTRODUCTION 1
2. AIMS: 1
3. LITERATURE SURVEY 2
  3.1. Polymer films 2
    3.1.1. Film coating 2
    3.1.2. The coating liquid 3
  3.2. Positron annihilation lifetime spectroscopy (PALS) 4
  3.3. Pellets: 5
  3.4. Process Analytical Technology (PAT) and factorial design 7
4. Section I. 7
  4.1. Sedimentation studies 8
    4.1.1 Materials 8
    4.1.2. Methods and results 8
    4.1.3. Discussion 11
  4.2. Evaluation of factors affecting the mixing of a polymer dispersion and a pigment suspension 12
    4.2.1 Materials 12
    4.2.2. Methods and results 12
    4.2.3. Discussion 19
5. Section II 20
  5.1. Testing of the structure of macromolecular polymer films containing solid active pharmaceutical ingredient (API) particles 20
    5.1.1. Materials 20
    5.1.2. Methods 20
    5.1.3. Results 24
    5.1.4. Discussion 31
6. Section 3 32
  6.1. Section 3/I. 32
    6.1.1. Materials 32
    6.1.2. Methods 32
    6.1.3. Results 35
    6.1.4. Discussion 42
  6.2. Section 3/II 42
    6.2.1. Materials 42

6.2.2. Methods 43
6.2.3. Results 44
6.2.4 Discussion 46
6.3 Section 3/III. 46
6.3.1 Materials and methods 46
6.3.2. Dissolution studies 47
6.3.3. Results 47
6.3.4. Discussion 49
7 FINAL CONCLUSION, NOVELTY, PRACTICAL USEFULNESS 49
8 References 50
Acknowledgement 57

ABREVIATIONS:

API: Active Pharmaceutical Ingredient

PALS: Positron Annihilation Lifetime Spectroscopy

MFFT: Minimal Film Forming Temperature

DSC: Differential Scanning Calorymetry

TG: Termogravimetry

SE: Surface free energy

PAT: Process Analytical Technology

LI-II.: Laboratory scale I-II.

MCC: Microcrystalline Cellulose

RH: Relative humidity

$S_{12 \text{ or } 21}$: Spreading Coefficient

1. INTRODUCTION

The aim of research in pharmaceutical technology is to produce effective dosage forms that possibly have no side effects. The dissolved active agent should bind to the receptor in optimal amount.

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 pharmaceutical dosage forms in therapy. They play an important role in the pharmaceutical industry because about 80% of the medicines are of solid dosage form. 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. Formulation of matrix pellets by extrusion-spheronization is another option for sustained release that is demonstrated in this study.

For an understanding of these processes, a deep investigation of the interactions between the applied materials and equipment, and of 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. The effects of conditions (mixing volume, dimensions of the mixing tank, type of mixing apparatus, stirring time, stirring speed, etc.) must be evaluated. 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. LITERATURE SURVEY

3.1. Polymer films

Polymer films play a very important role in the production of certain pharmaceuticals, e.g. coated and modified-release dosage forms. The objective of these orally administered forms is to control the release of the therapeutic agent and hence the drug absorption from the gastrointestinal tract. Such a dosage form effectively reduces adverse effects associated with peak plasma concentrations beyond that needed for therapeutic effectiveness, while maintaining the plasma level above or at that needed to achieve the therapeutic effect for a longer period.

Another important field is mucoadhesive films, where the API incorporated in the film layer is absorbed from the buccal mucosa in order to achieve a local (e.g. antibacterial) or a rapid systemic effect, avoiding the first-pass effect [1-3].

During the preparation of a coating layer, it is necessary to know its physicochemical properties, e.g. its glass transition temperature, minimum film-forming temperature, flexibility and surface properties, how the API particles are located in the structure of the film-forming polymer and whether these particles modify the properties of the film formed [4]. The APIs in the film layer are mostly in solid form and rarely in dissolved form; the particle size of the API is therefore crucial, and the use of microcrystalline forms is recommended.

3.1.1. Film coating

This process was developed in the early 1950s to help resolve many of the problems associated with sugar coating which is rigid, hygroscopic, and it moulders.

Film coating involves the deposition usually by spray method, of a thin film of polymer surrounding the dosage form core [5].

The film-forming materials can be used as solutions, emulsions or suspensions (aqueous dispersions) [6]. Film formation from solutions is a relatively simple process. The droplets of the spray fluid must, however, be able to spread on the surface and coalesce to a liquid film and should therefore be sprayed with care. For this reason, evaporation of solvent in the spray must be limited to prevent any major viscosity increase in the droplets or even spray drying of some of the smaller ones.

Because of the curing of coated products, the thermal and mechanical sensitivities and also the stability and the compatibility problems induced by the special system and the compulsory additives (emulsifying agents), the processibility of aqueous dispersions is more complex than that of solution systems [7-10].

Organic solutions of polymers were earlier widely used but these systems are nowadays less popular because of the environmental problems and the danger involved in the process. The applicability of aqueous solutions is restricted by solubility of the polymers. In effort to replace organic solvents in processes with water-insoluble film formers, the polymers proven as pharmaceutical coating agents have been further developed as dispersed aqueous systems [11].

3.1.2. The coating liquid

The widely used coating liquids contain a pigment suspension and a polymer dispersion. The first step in the suggested mixing sequence for the preparation of these liquids is the preparation of the pigment suspension which must then be gently mixed with the polymer dispersion.

In addition to the polymer, the film contains plasticizers and colorants which are needed to achieve the desired properties in the dosage form.

Various types of polymers (cellulose derivatives, poly(methacrylates), poly(vinyl) derivatives, etc.) can be used to form aqueous dispersions but the best-evaluated are acrylic acid derivative polymers.

Numerous water-soluble and insoluble additives (plasticizers, colorants, pigments, antifoaming agents, etc.) are utilized to change the properties of films and to increase the processibility of these liquids. The water-insoluble additives are applied in these aqueous dispersions for the preparation of polymer films for different purposes. It is recommended to add an insoluble glidant (e.g. talc, magnesium stearate) to the suspension to avoid sticking [12]. Insoluble pigments (e.g. iron oxide, titanium dioxide) are also applied to ensure the appropriate appearance of the coated product. They can modify the properties of the film formed [4] and thus their homogeneous distribution is indispensable.

The suggested mixing sequence for the preparation of coating liquid containing insoluble particles is very important. According to a manufacturer of dispersions, the first step is the preparation of the pigment suspension [13]. In this case, the intensive homogenization of the materials (glidants, pigments, plasticizers and other excipients) in water must be performed with a high-speed mixing apparatus. After this, the freshly prepared homogeneous pigment suspension must be gently mixed with the acrylic dispersion. High-speed mixing can cause precipitation of the polymers, and this apparatus can therefore not be used in this step [14]. The even distribution of the insoluble particles in the pigment suspension is very important because gentle mixing cannot disrupt pigment aggregates. The main cause of problems during the preparation of these liquids is the fact that the definition of “gentle mixing” is not clear-cut.

3.2. Positron annihilation lifetime spectroscopy (PALS)

Positrons are the antiparticles of electrons. When a positron meets an electron, they undergo mutual annihilation and provide information on the surroundings of the annihilating pair. In materials, the probability of such a meeting depends on the electron density around the positron. In polymers, the electron density at any site is determined by the vicinity of polymeric chains; hence, positrons are exceptionally sensitive to free volumes.

In polymers, a large proportion of injected positrons form a bound state with electrons before their annihilation [15]. One of the bound states, the *ortho*-positronium atom or *o*-Ps, has a ‘‘long’’ lifetime: in polymers it lives for 1–3 ns. This lifetime is long enough for *o*-Ps atoms to scan their surroundings and, fortunately, it is long enough to be conveniently observed. Moreover, according to a simple model, the lifetime of an *o*-Ps atom depends on the size of the free volume in which it is located ([16] Eq.(1))

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \qquad (1)$$

Here, τ is the lifetime of the *o*-Ps, R is the radius of the (expectedly) spherical free volume holes and ΔR is a constant. The equation indicates that the lifetime of *o*-Ps atoms increases with the size of the free volume holes.

The above equation provides the most important tool to gain information on a polymeric sample by positron lifetime spectroscopy. The *o*-Ps lifetime is directly correlated with the size of free volume holes in the material. Thus, any change in the free volume is reflected in the *o*-Ps lifetime. Although the chemical composition of a certain polymer may affect the lifetime a little [17], *o*-Ps atoms provide the most direct information on the size of free volume holes for polymers.

There are two ways to gain information on free volumes from PALS spectra. The easier is to assume that every *o*-Ps atom sits in uniform holes before annihilation. Although this assumption is definitely wrong for amorphous polymers, it provides a stable average lifetime (and free volume size). Moreover, this average lifetime reacts subtly to the changes of the free volume.

The other possibility is to try to find the exact lifetime distribution. However this requires much more calculations and sometimes provides unstable intensities, the obtained results usually worth the efforts. By this method, we can get a more detailed information on the distribution of the size of free volume holes, i.e., on the arrangement of polymeric chains [18-21].

3.3. Pellets

Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications [22]. Interest in pellets as a dosage form (filled into hard capsules or compressed into tablets) has increased continuously as their multiparticulate nature offers important pharmacological and technological advantages over conventional single-unit solid dosage forms [23-29].

Several methods are applicable for pellet preparation, the most popular being solution/suspension layering, powder layering, direct pelletization with the use of high-shear mixers and conventional or rotary fluid-bed granulators, and extrusion-spheronization. These pelletization techniques have been reviewed in detail in a number of papers [26, 30-33].

As this thesis focuses on the extrusion–spheronization process, this multistep technique is briefly outlined below. Furthermore, extrusion refers only to wet extrusion; melt extrusion and solid-lipid extrusion are not considered. This process involves several distinct preparation phases: a uniform powder mixture of drug and excipient(s) is wet-massed by the addition of a liquid binder, followed by pressing of the moistened mass through an extrusion screen (extrusion) to form cylindrical extrudates, which are subsequently broken into smaller cylindrical rods and rounded into spherical granules by means of a fast-rotating friction plate (spheronization) and finally dried. This process is an efficient technique for the manufacturing of pellets (even for formulations with a high drug load), and allows a high throughput based on the continuous nature of the extrusion process when combined with multiple spheronizers operating in parallel or in series. A comprehensive review of this technique [33] details the different steps of the process and the effects of the different process parameters on the pellet quality at each stage of the extrusion–spheronization process. In view of the specific nature of this process, not all moistened powder mixtures can be successfully extruded and spheronized. Newton [34] defined the specific requirements for a wetted mass to be suitable for extrusion and spheronization, based on the pioneering papers of Reynolds [35] and Conine and Hadley [36]. To allow extrusion, a cohesive plastic mass must be formulated that remains homogeneous during extrusion. The mass must possess inherent fluidity, permitting flow during extrusion, and self-lubricating properties as it passes through the die. The resultant strands of extrudates must not adhere to each other, and must exhibit plasticity so that the shape imposed by the die is maintained.

The requirements for spheronization of the cylindrical extrudate are as follows: (a) the extrudate must possess sufficient mechanical strength when wet, yet it must be brittle enough to be broken down to short lengths in the spheronizer, but not so fragile that it disintegrates completely; (b) the extrudate must be sufficiently plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate in the spheronizer; and (c) the strands of the extrudates must not adhere to each other so that the particles do not aggregate during spheronization [34, 37-39]

In relation to the above-mentioned requirements of the wetted mass, microcrystalline cellulose (MCC) is incorporated in most formulations that are processed via extrusion-spheronization, since it provides the wetted mass with appropriate rheological properties [34] for successful extrusion and spheronization [40]. Its good binding makes MCC the gold standard as an extrusion–spheronization aid, providing cohesiveness to a wetted mass containing MCC [41-45].

Furthermore, it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity [46], thereby facilitating extrusion, improving the wetted mass plasticity and enhancing spheronization [47]. Moreover, by controlling the movement of water through the plastic mass, it prevents phase separation during extrusion or spheronization [48]. As a consequence of these properties, MCC-based pellets produced via extrusion–spheronization exhibit good sphericity, low friability, high density and smooth surface properties. Furthermore, from a processing aspect, relatively wide ranges of water content and processing parameters can be employed to provide pellets with acceptable quality, as an indication of the robustness of the formulations.

Various pharmaceutical excipients can be used to modify the liberation of an active agent from the pellets formulated by extrusion and spheronization. These components form a matrix system, which ensures appropriate liberation. Different types of polymers can be used to form soluble or insoluble systems. Their properties and the interactions between the components influence the dissolution of the active pharmaceutical ingredient. The film formation in the solid polymer matrix significantly influences the texture of the dosage form and hence the liberation of the active agent.

3.4. Process Analytical Technology (PAT) and factorial design

Understanding a process leads to the ability to identify the critical control points. This information is necessary for the application of Process Analytical Technology. PAT cannot only lead to a better manufacturing process but also speed up the research and development [49-50].

The factorial design is a method often used to accelerate the solution of problems. This method has been utilized in various branches of science and industry, e.g. food research [51], environmental management [52], chemistry [53] and pharmaceutical technology [54-58] The mathematically determined effects of different factors are compared by means of this technique, this information being very useful for the application of process analytical technology, at the heart of which is the acquisition of a deep understanding of the manufacturing process [59].

4. 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.

4.1. Sedimentation studies

4.1.1 Materials

Commercial titanium dioxide (Merck GmbH, Darmstadt, Germany) was used in which the particles form aggregates. It was dispersed in distilled water at a concentration of 10%.

4.1.2. Methods and results

4.1.2.1. Factorial design

The fluid was stirred in glass beakers with identical dimensions (7.7 cm in diameter) with an Ultra-Turrax mixer (IKA Ultra-Turrax T25 basic, IKA-Werke GmbH & Co. Kg, Staufen,Germany). The diameter of the turbine was 1.85 cm. The turbine of mixer was located in the midst of container. A 2^3 full factorial design was applied for different mixings; the factors were the stirring rate (X_1), the stirring time (X_2) and the volume (X_3), with the levels to be seen in Table 1.

Table 1: Levels of factors

Factor	Low (-)	Zero (0)	High (+)
X_1	9500 rpm	13500 rpm	17500 rpm
X_2	5 min	7.5 min	10 min
X_3	100 ml	150 ml	200 ml

The eight experimental set-ups were supplemented with a central point. Statistica for Windows 6.1 AGA (StatSoft, Inc. Tulsa, USA) software was applied to determine the effects of the factors. The following linear approach was applied to determine the surface of the response:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

The b_0 (intercept) is the mean for y value of nine samples.

4.1.2.2 Determination of titanium dioxide content

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 (PW 4025/00, Minipal Philips, Almelo). This compact table-top instrument can be used to measure the elemental range from sodium (Na) to uranium (U), in the concentration range from ppm to 100%, and it ensures very rapid and facile data acquisition.

The conditions applied during the measurements were 8 kV, 120µA and an air purge with a kapton filter. The samples were measured for 20 s. The linearity of calibration was checked between the titanium content of 4–12% (6.6–20% of titanium dioxide). The R^2 was 0.9827. The accuracy of the method was checked with liquids containing a certain amount of titanium dioxide. The difference between calculated and measured concentration was not significant (t- test, $p < 0.05$). The pigment suspensions poured into the sample holder and they were tested directly without withdrawing. Three parallel tests were performed. The sedimentation curves were constructed from the measured data. The maximum in the sedimentations when the concentration reached the highest level was taken as 100%. The other results were calculated from the concentration ratios. The fitting revealed that these curves can be described by the Weibull model [60]. A non-linear fitting approach with the following equation (Eq. 2) was applied:

$$M = M_0 \left\{ 1 - \exp\left[- \frac{(t - T)^{\beta}}{a} \right] \right\} \tag{2}$$

where M is the percentage sedimentation up to time t, M_0 the maximum percentage sedimentation, T the delay time, β the shape parameter, and a is the scale parameter. The characteristic sedimentation time ($t_{63.2\%}$), i.e. the time necessary to reach 63.2% of the maximum enrichment of titanium dioxide, was determined from the curve.

The enrichment of titanium dioxide at the bottom of the sample holder was readily measured with this very rapid test method. It can be seen from the sedimentation profile that there were no fundamental differences between the characteristics of the sedimentation curves, but the courses were not identical, e.g. the maximum sedimentation was reached at 15 min for S1 and at 35 min for S4 (Fig. 1).

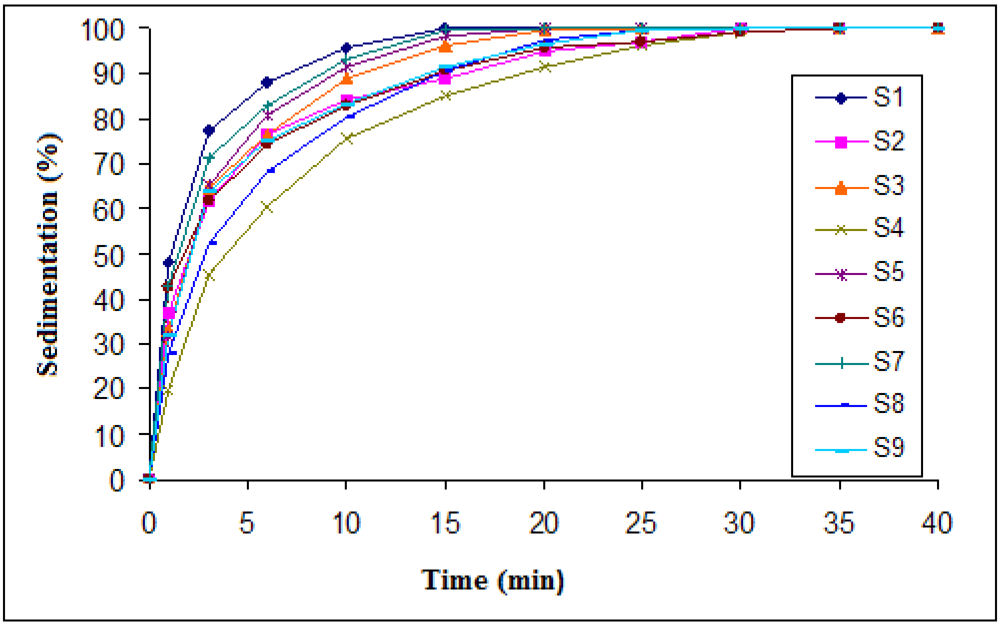

Fig. 1. Sedimentation curves for pigment suspensions

The fittings were very good, because the R^2 values were higher than 0.99. The results derived from the fitting were different for the different samples (Table 2). Since the characteristic sedimentation time of the sample with a low mixing rate and a low mixing time was very short, the addition of this suspension to the polymer dispersion must be very quick. Accordingly, increase of this time is inevitable. An appropriate combination of the factors can cause a threefold increase in the sedimentation time (see Section 3 for S1 and S4). The values of the shape parameters (β) are less than 1, and thus the curves are saturation curves with a fast initial increase.

Table 2: Kinetic study parameters

Sample	**X_1**	**X_2**	**X_3**	**$t_{63.2\%}$ (s)**	**Correlation**	***a***	**β**
S1	-	-	-	2.03	0.9968	1.74	0.9613
S2	+	-	-	4.28	0.9957	3.79	0.9068
S3	-	+	-	2.90	0.9969	2.75	0.9289
S4	+	+	-	6.69	0.9955	4.42	0.8975
S5	-	-	+	2.89	0.9967	2.45	0.9398
S6	+	-	+	4.29	0.9952	3.61	0.9014
S7	-	+	+	2.42	0.9972	2.13	0.9468
S8	+	+	+	6.03	0.9955	3.94	0.9102
S9	0	0	0	3.92	0.9971	3.38	0.9130

The values of the scale parameter (*a*) indicate the speed of increasing of the curve. The higher the value is, the slower the sedimentation is. The highest one was detected for S4 (just as it was seen at the sedimentation time).

The characteristic sedimentation times were compared by means of the factorial design. The linear estimation with the interactions was very good (R = 0.9998). Table 3 presents the ranked order of the factors. The stirring rate, the time and the interaction of these factors were significant in the 99% confidence interval. The higher are the values of these factors, the longer is the sedimentation time. Change of the stirring rate can cause a more than twofold increase in the sedimentation time relative to the increase caused by change of the stirring time. The sample volume on this laboratory scale was not a significant factor, but it can be concluded that increase of the volume decreases the sedimentation time. This statement is indicated by the negative sign of the coefficients for volume and the two-factor interaction containing the mixing volume.

The three-factor interaction was less relevant. The positive sign in the equation of the response surface indicates a slight increase in the sedimentation time.

Table 3: Factorial design parameters

Factor	Coefficients
b_0	3.9388*
b_1	1.3813*
b_2	0.5688*
b_{12}	0.4687*
b_{23}	-0.2513
b_{13}	-0.1288
b_{123}	0.0837
b_3	-0.03375

4.1.3. Discussion

It can be concluded that the change in the concentration of titanium dioxide can be detected by energy-dispersive X-ray fluorescence analysis. In a pigment suspension without additives, the sedimentation is a very quick process, which can be described by the Weibull model. The sedimentation of this pigment suspension can be changed via the appropriate parameters of the Ultra-Turrax mixer. The application of this rapid test method and the determination of the characteristic sedimentation time allowed comparison of the effects of different technological parameters [61]. This information is indispensable for a more accurate knowledge of the preparation of the coating fluid and for detection of the critical control point of coating. Accordingly, their precise control can promote the formulation of a coating fluid and the occurrence of the coating process with less chance of disturbing effects.

4.2. Evaluation of factors affecting the mixing of a polymer dispersion and a pigment suspension

4.2.1 Materials

Titanium dioxide (Merck GmbH, Darmstadt, Germany) was applied as an insoluble material. It was dispersed in distilled water at a concentration of 10%. Eudragit NE 30D (Evonik Röhm GmbH, PharmaPolymers, Darmstadt, Germany) was applied as a polymer dispersion. Eudragit NE 30D contains 28.5-31.5% dry matter (poly (ethyl acrylate, methyl methacrylate) 2:1) and approximately 1.5% Nonoxynol 100 as emulsifier. Eudragit® NE 30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate that is highly suitable for sustained-release film coatings [62] and for sustained release granules [11, 63]. It is insoluble in water, displays low permeability and pH-independent swelling, and is highly flexible [13].

A number of physical and chemical stability problems are associated with the use of Eudragit NE [4, 64-65].

The composition of the liquids was as follows: 20% pigment suspension, 30% polymer dispersion and 50% purified water.

4.2.2. Methods and results

4.2.2.1. Factorial design

The pigment suspension was prepared with an UltraTurrax mixer according to our previous results (quantity: 100 g; stirring speed: 17,500 rpm; time: 10 min) [61]. The fluid was mixed in identical cylindrical glass beakers (7.70 cm in diameter) with a magnetic stirrer (IKA-Werke GmbH & Co. Kg, Staufen, Germany). The mixing sequence was as recommended by the manufacturer (the pigment suspension was added to the polymer dispersion). A 2^4 full factorial design was first applied to optimize the mixing of the polymer dispersion and the pigment suspension (Table 4); the factors included were the quantity, the stirring time, the motor stirring speed and the stirrer size (in grams).

Secondly a 2^3 full factorial design with a central point was used to determine the factors affecting the volume of the mixing whirlpool (Table 4). The factors were the quantity, the stirring speed and the stirrer size. The values of the factors were similar to those in the previous evaluation.

Statistica for Windows 7.1 AGA (StatSoft, Inc. Tulsa, USA) software was applied to determine the effects of the factors. The experiments were performed in randomized sequence. The following linear approach was applied to determine the surface of the response for the 2^3 factorial design:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

while that used to determine the surface of the response for the 2^4 factorial design was:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{123}X_1X_2X_3 + b_{234}X_2X_3X_4 + b_{124}X_1X_2X_4 + b_{134}X_1X_3X_4$$

Table 4: Levels of factors

Factor	**Low (-)**	**Zero (0)**	**High (+)**
Quantity (X_1)	100 g	150 g	200 g
Time (X_2)	10 min	15 min	20 min
Stirring speed (X_3)	400 rpm	700 rpm	1000 rpm
Stirrer (X_4)	1.73 g (ca. 0.6cm^3)	2.65 g (ca. 0.9 cm^3)	3.43 g (ca. 1.2 cm^3)

4.2.2.2. Determination of homogeneity

The solid content at the bottom of the sample holder was determined by a gravimetric method: 5 ml of liquid was taken out with an automatic pipette. The sampling sites were similar (at the bottom of the beaker, next to the wall). The samples were dried at 105 °C in a heating chamber. The liquids and the dried samples were weighed with an analytical balance. Three parallel measurements were performed. 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 absolute value of relative deviation can be calculated according to the following equation (Eq. (3)).

$$(\text{average measured concentration} - 17.033) \times 100/17.033 \qquad (3)$$

It can be seen from the results of the homogeneity tests that the deviation of the solid content from the calculated value exhibited great variation (0.01-24.25%) (Table 5).

Table 5: Relative deviation of solid content of samples

Quantity (g)	**Time (min)**	**Stirring speed (rpm)**	**Stirrer (g)**	**Relative deviation (%)**
100	10	400	1.73	17.30
200	10	1000	1.73	1.25
100	20	1000	1.73	0.17
200	10	400	3.43	15.75
200	20	400	1.73	11.25
100	10	400	3.43	1.75
100	20	400	3.43	17.00
200	10	1000	3.43	0.01
200	20	400	3.43	20.75
100	20	400	1.73	14.75
100	10	1000	1.73	4.33
100	20	1000	3.43	3.50
200	10	400	1.73	24.25
200	20	1000	1.73	2.50
200	20	1000	3.43	1.00
100	10	1000	3.43	9.33

The determination of the response surface (R^2=0.9991) demonstrated the relative importance of the various factors (Figure 2).

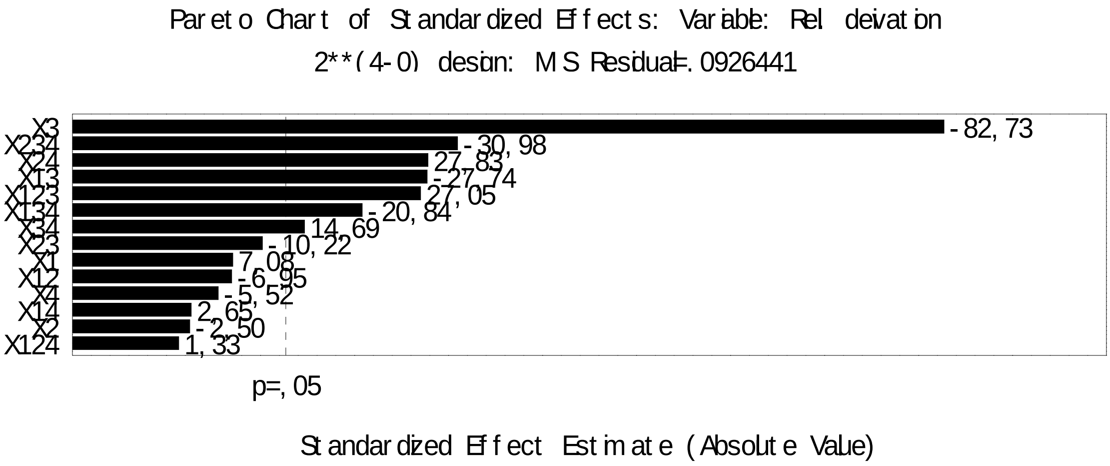

Figure 2: Effects of various factors on relative deviation

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.

4.2.2.3 . Study of the vortex cone

Callipers with an accuracy of 0.02 mm were used to determine the volume of the whirlpool induced by mixing. The height of the liquid was measured during homogenization and without the mixing. The volumes were calculated from the results. The difference in these parameters can be attributed to the volume of the vortex cone generated by the turbulent movement of the stirrer.

The thickness of the foam was also measured with these callipers with an accuracy of 0.02 mm. Three parallel measurements were performed.

Because of the large number of parameters, an exact mathematical description of the motion of the liquid is very difficult, and the choice of the optimum technological parameters for the production of a homogeneous fluid is not easy. Very sophisticated or indirect (less exact) methods can be used for their determination. An important feature of the motion of the liquid is the vortex formed during mixing. The volume of this vortex can be easily determined during homogenization. Accordingly it was chosen for evaluation as an investigated parameter in this study. The previously used factors (except time) were also applied (see 4.2.2.1.). The explanation of the exception was that this factor was the least important individual one. The liquid and the values of the factors were the same as in the homogeneity testing.

It can be seen from the results that the vortex volume varied considerably (0.335 – 6.527) with the different set-ups (Table 6).

Table 6: Volume of the vortex cone

Stirring speed (rpm)	**Stirrer (g)**	**Quantity (g)**	**Vortex volume (cm^3)**
400	1.73	100	1.549
1000	1.73	100	3.787
400	3.43	100	0.335
1000	3.43	100	6.527
400	1.73	200	0.457
1000	1.73	200	1.967
400	3.43	200	0.448
1000	3.43	200	4.566
700	2.65	150	1.237

The effects of the factors also differed greatly. The highest value was detected for the mixing speed (Figure 3). The fitting was very good (R^2=0.9632), but the factors and their interactions were not significant.

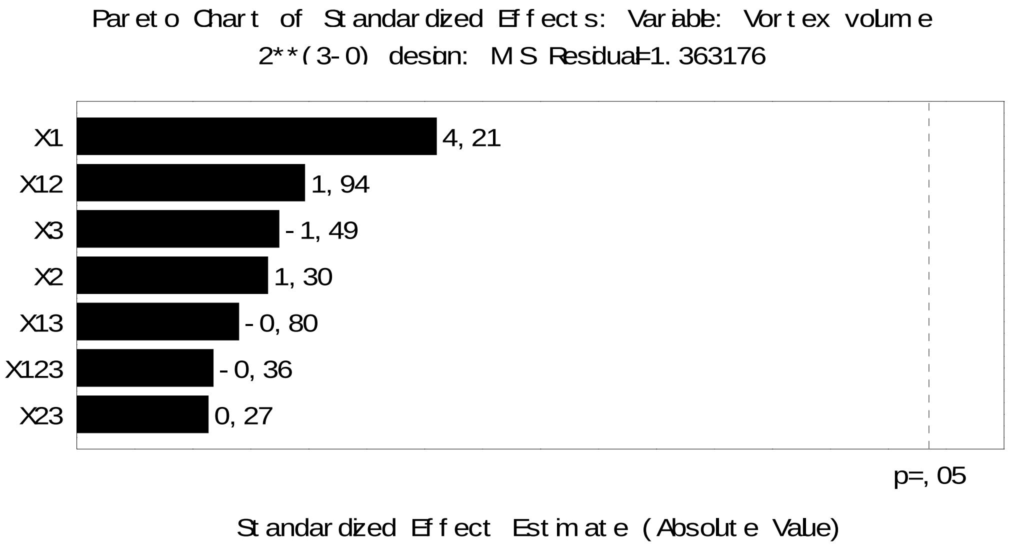

Figure 3: Effects of the various factors on volume of vortex cone

The effects of the factors in the homogeneity tests and the vortex cone were compared. It can be concluded that there was no obvious connection between the results of the two experiments (Figure 4).

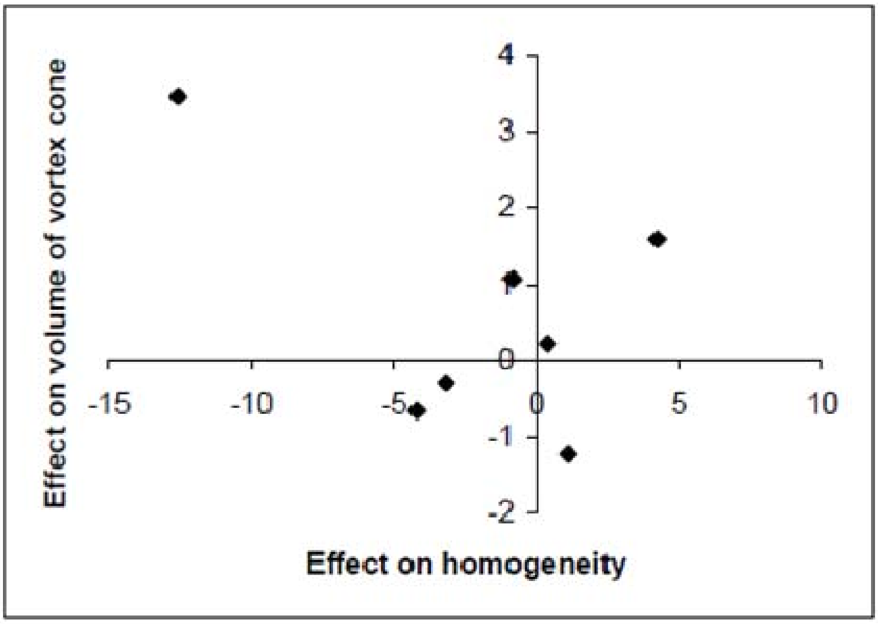

Figure 4: Comparison of effects of factors

The explanation of the difference can be observed during the stirring of the water (Figure 5). It can be seen that not only the size of the cone differed, but also its shape. The height of the cone was similar, but it was narrower for the smaller stirrer. The difference was more relevant than the change in the volume.

The altered shape led to differences in the surface of the liquid, which can induce additional problems, e.g. the greatest higher possibility of foaming and evaporation of the liquid, etc. The thickness of the foam at the wall of the mixing tank was determined for 200 g of coating liquid. A higher speed (1000 rpm), the larger stirrer induced thicker foam (Figure 6). This can be explained by the wider vortex cone, which exhibited a larger surface.

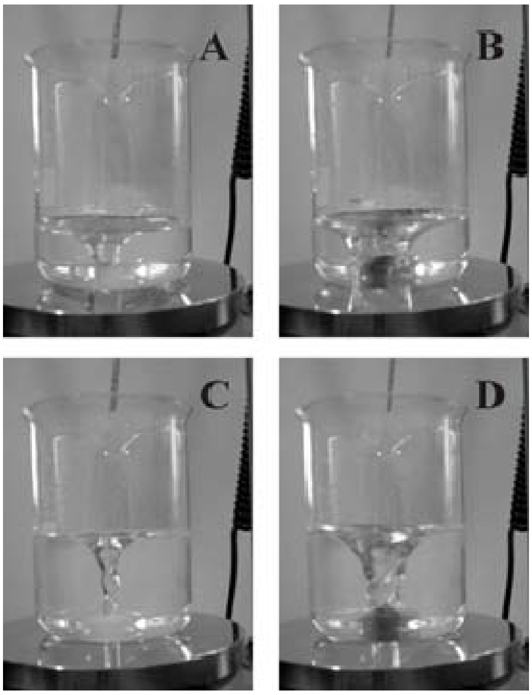

Fig. 5: Comparison of the vortex cone during the stirring of water

(A - quantity: 100 g; stirrer: 1.73 g; B - quantity: 100 g; stirrer: 3.43g;

C- quantity: 200 g; stirrer: 1.73 g; D - quantity: 200 g; stirrer: 3.43g)

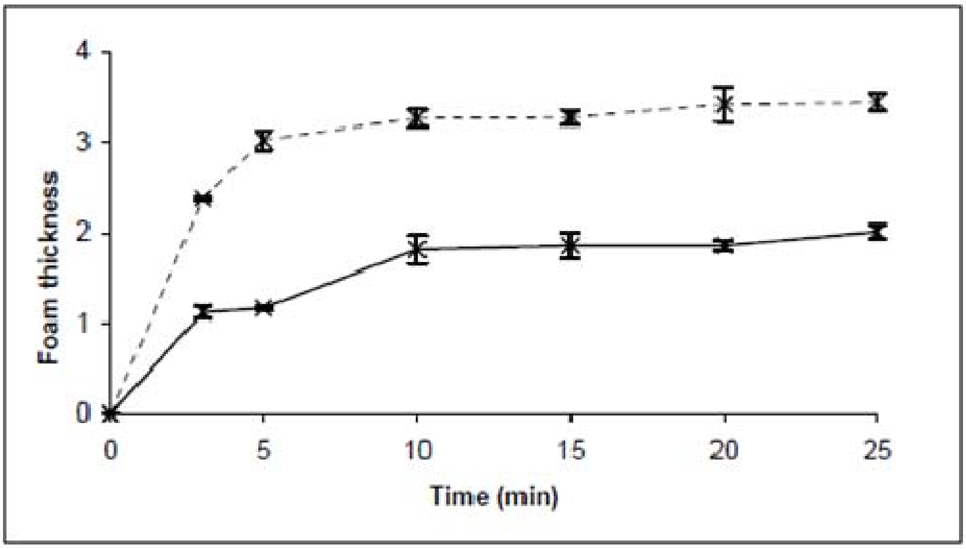

Fig. 6: Change in foam thickness as a function of time (continuous line - 1.73g stirrer, dashed line - 3.43 g stirrer)

4.2.2.4. Study of evaporation

Evaporation of a similar composition containing a volatile component (ethanol) was also studied where the effect of an antifoaming agent (Dimethicon) was measured [66]. In consequence of to its low interfacial tension, it can form a layer on the surface of a liquid, and the effect of this was studied by determination of the quantity of the stirred liquid that was evaporated. The effects of different operational factors were compared by means of factorial designs.

It was concluded that 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.

4.2.3. Discussion

During mixing, the liquid must be in constant motion for the homogeneous distribution of the insoluble particles. Previous results revealed that the factors affecting intensiveness of moving were more important 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. These factors can be changed in different ways e.g. it is well known that the viscosity depends on the shearing and also the temperature [5].

Overall, it can be concluded 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 [67].

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 [66].

5. Section II

5.1. Testing of the structure of macromolecular polymer films containing solid active pharmaceutical ingredient (API) particles

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.

5.1.1. Materials

Eudragit® L 30D-55 (Evonik Röhm GmbH, PharmaPolymers, Darmstadt, Germany), is an aqueous dispersion of anionic polymers with methacrylic acid functional groups. The coating liquid compositions contained titanium dioxide, talc, triethylcitrate (the suggested ratio for Eudragit® L [10]), dimethicon (type E1049, a gift from EGIS Pharmaceuticals Plc., Budapest, Hungary) as antifoaming agent, and microcrystalline diclofenac sodium (Amoli Organics Pvt. Ltd., Gujarat, India) in different proportions as API. The use of microcrystalline form is important in case of coating, because greater particles can block the nozzle during atomizing. Table 7 presents the composition of the samples.

Table 7: Composition of the samples

		Film 1	**Film 2**	**Film 3**
I	**Diclofenac sodium**	0.00 g	1.00 g	5.00 g
	Talc	6.56 g	6.49 g	6.23 g
	Titanium dioxide	1.79 g	1.77 g	1.70 g
	Triethyl citrate	1.31 g	1.30 g	1.24 g
	Dimethicon	0.34 g	0.33g	0.32 g
	Purified water	28.34 g	28.05 g	26.92 g
II	**Eudragit® L 30D-55**	33.34 g	33.00 g	31.67 g
	Purified water	28.34	28.05	26.92

5.1.2. Methods

The solid content of each coating dispersion was 20%. The first step was the preparation of the pigment suspension [13]. The pigment suspension containing 0%, 1% or

5% of the API was prepared through Ultra-Turrax (IKA-Werke GmbH & Co. KG, Staufen, Germany) mixing (17,500 rpm) for 10 min. After this, the suspension was poured into the polymer dispersion and mixed with an overhead stirrer (IKA-Werke GmbH & Co. KG) at 210 rpm for 15 min [66]. As a final step, the mixture was sieved. The ready coating liquid was tested with an MFFT apparatus. The free films were prepared by pouring the mixture onto a Teflon surface, and drying it at room temperature (24±1°C, 37% RH) for 48h. Deformation tests were performed 1 day after preparation. Ten to 12 mg samples of the cast films obtained and the API were used for differential scanning calorimetry (DSC) analysis. The films were also tested by PALS after various storage periods (1, 2 or 3 weeks at 17°C and 65% RH). Other free films were formed on a glass surface and dried under the same circumstances. These free films were tested with an OCA 20 optical contact angle-measuring instrument (DataPhysics Instruments GmbH, Filderstadt, Germany). The surface roughness of Film1 formed on a glass surface was examined. DSC and thermogravimetric (TG) analyses of the API were also performed.

5.1.2.1. Minimal Film Forming Temperature (MFFT)

To study the MFFT of the coating liquid, a Rhopoint MFFT apparatus (Rhopoint Instruments Ltd., Bexhill-on-Sea, UK) was used. The MFFT is the lowest temperature at which a latex, emulsion or adhesive will uniformly coalesce when laid on a substrate as a thin film. An accurate MFFT value allows the formulation of products that cure correctly under specified application conditions. Three parallel tests were performed on each sample.

5.1.2.2. Deformation process

A breaking hardness tester was used to evaluate the deformation (breaking) process of the free films. The apparatus and the software were developed in our department. The apparatus contains a special specimen holder and a jowl, and it is connected to a computer via an interface. Thus, not only can the ultimate deformation force be measured, but the process (force—time and force—displacement curves) can also be followed. The film is located horizontally on a special ring and the jowl moves vertically. If the measured plot (force—time) is parallel to the x-axis, the deformation is viscoelastic; if the plot rises linearly, the deformation is elastic. Parallel tests were carried out.

5.1.2.3. *Evaluation of surface roughness*

The surface roughness of Film1 was determined with a Mitutoyo SJ-201P tester (Mitutoyo Co., Kawasaki, Japan). An evaluation length of 2.5 mm was applied. For this test, free films were prepared. The liquid was atomized onto a glass surface. The arithmetic mean deviation (Ra), root-mean-square deviation (Rq), and maximum height of the profile (Rz) were determined [68]. 10 parallel tests were performed. There was no need for the examination of the other films because the pretreatment of pigments and API was the same in case of all films.

5.1.2.4. *Contact angle measurements*

The wetting process of free films was observed with an OCA 20 optical contact angle measuring instrument (DataPhysics Instruments GmbH, Filderstadt, Germany). The liquids were dispensed through a microsyringe. To investigate the changes in surface energy, diiodomethane (drops between 2 and 3 μL) was used, together with purified water. Data were collected and analysed with SCA instrumental software, and also Microsoft Excel. The interactions of the drops with the surface were monitored with a CCD camera, with a time step of 1 s between successive acquisitions. The measuring accuracy of the video system was ±0.1 s. The contact angles reported are based on the averages for 10 static drops in different areas on the surfaces of the films, and 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) [69].

In the method of Wu, the SE is taken as the sum of dispersive (d) and polar (p) components. The SEs of solid materials can be determined by means of contact angle measurements on two liquids with known polarities. They can be assessed by solving two equations with two unknowns Eq. (4):

$$(1+\cos\Theta)\gamma_l = \frac{4\left(\gamma_s^d \gamma_l^d\right)}{\gamma_s^d + \gamma_l^d} + \frac{4\left(\gamma_s^p \gamma_l^p\right)}{\gamma_s^p + \gamma_l^p} \qquad (4)$$

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension.

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. The spreading coefficient of the coating liquid over the API (S_{12}) and that of the API over the film layer (S_{21}) can be determined according to Eqs. (5) and (6) [70]:

$$S_{12} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}\right] \tag{5}$$

$$S_{21} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_2}{2}\right] \tag{6}$$

The work of adhesion and the SE may be calculated from each other [71, 72]. According to Dupré [73], the work of adhesion ($\Delta\gamma_a$) describes the work necessary to separate two phases so that two new surfaces of unit area are formed, but from different materials. The work input must compensate for the surface free energies (γ_{s1} and γ_{s2}) of the new surfaces. However, through the separation of the solid–solid interface, the work is lower by the interfacial energy ($\gamma_{s1,s2}$) as in Eq. (7):

$$\Delta\gamma_a = \gamma_{s1} + \gamma_{s2} - \gamma_{s1,s2} \tag{7}$$

The work of adhesion (W_a) is equal numerically to the energy that arises when two surfaces come into contact Eq. (8):

$$W_a = 4\left[\frac{\gamma_d^A \gamma_d^B}{\gamma_d^A + \gamma_d^B} + \frac{\gamma_p^A \gamma_p^B}{\gamma_p^A + \gamma_p^B}\right] \tag{8}$$

5.1.2.4. Differential Scanning Calorimetry (DSC)

The DSC curves of the free films were studied with a Mettler Toledo DSC 821e instrument (Budapest, Hungary). The start-temperature was 25°C, the end-temperature was 300°C and the heating rate was 10°C/min. After the end–temperature was reached, the samples were refrigerated to 25°C and reheated to 300°C. An argon atmosphere and aluminium pans were used.

5.1.2.5. Thermogravimetry (TG)

The TG curves of the API were studied with a Mettler Toledo instrument. The method used for DSC was applied.

5.1.2.6. Positron lifetime measurements

The positron source applied for the measurements was made of carrier-free ^{22}NaCl. In this case, the radioactive nuclide ^{22}Na, emits positrons which penetrate the sample material. The active ^{22}NaCl was sealed between two very thin (5μm) titanium foils, which ensured that 90-95% of the emitted positrons penetrated the studied polymer samples. The activity of the source was around 4×105 Bq.

Positron lifetime spectra were recorded with a fast–fast coincidence system [74]. The system was constructed from standard ORTEC electronic units, and detectors were made from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps. Spectra were collected in 4096 channels of a computer based multichannel analyser card. The channel time was around 10 ps.

The collected lifetime spectra, than, were evaluated and three lifetime components were extracted from them by the computer code RESOLUTION [75]. The shorter two of these lifetimes are very hard to interpret in polymers. They represent the annihilation of free and trapped positrons and the short living positronium state. In our study, we used the third component, the longest living positron state. This lifetime reflects the annihilation of *o*-Ps atoms and it is the most reliable parameter of lifetime spectra in the case of polymers. The intensity of this lifetime component was around 10 % and did not changed significantly during our study.

For the determination of lifetime distributions, we applied a variant of the code MELT [76]. This applies the maximum entropy method to determine lifetime distributions.

5.1.3. Results

Based on the experiments it was stated that the MFFT of these films was 24°C, which corresponds to the value given in the Eudragit brochure [13]. This means that the components had no effect on the MFFT of the bulk film.

The mechanical strength and the deformation of the free films can be described by deformation (breaking) curves (Fig. 7).

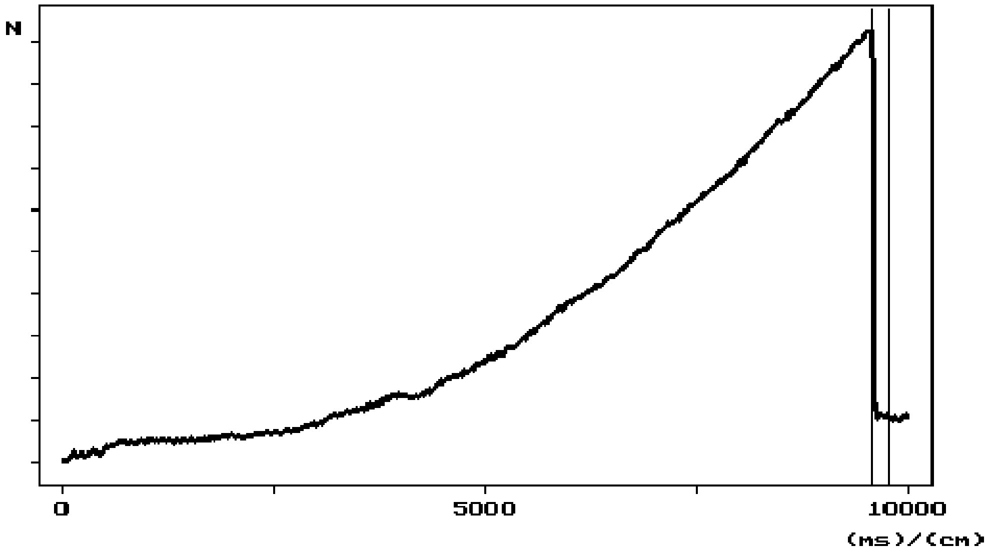

Fig. 7: Deformation curve of free film containing no active pharmaceutical ingredient (Film1)

These curves showed that these free films first undergo a viscoelastic deformation, which is followed by an elastic section, at the end of which breaking occurs. (Other polymers showed nearly the same behaviour.) Together with the increase in the content of the API, the strength of the films decreased considerably (Table 8). This means that the resistance and the processibility of the films were reduced. 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.

Table 8: Strength and thickness of free films

	API (%)	**Breaking force (N)**	**Thickness (mm)**
Film 1	0	10.66 ± 1.39	0.223 ± 0.022
Film 2	1	5.75 ± 1.05	0.212 ± 0.015
Film 3	5	2.85 ± 0.51	0.321 ± 0.030

Surface roughness of Film 1 was tested: Ra: 4.21 ± 0.98 µm; Rq: 5.47 ± 1.46 mm; Rz: 28.24 ± 6.52 mm. These results show the importance of the pretreatment of pigments [68].

Besides the deformability, knowledge of the surface properties of the polymer films is very important. SEs were calculated to describe the wetting process of the free films and the API (Table 9). Contact angles detected at 7 seconds were used for the evaluations. The SEs were much higher than those of the bulk film. It can be concluded that the content of API influenced the SEs of the free films. On 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.

Table 9: Surface free energies

	Film 1	**Film 2**	**Film 3**	**API**
SE (γ)	55.34	61.0	70.95	80.3
Dispersive (γ^d)	37.87	39.4	38.44	43.57
Polar (γ^p)	17.47	21.61	32.51	36.73
Polarity (%)	31.57	35.43	45.82	45.74
S_{12} (film on API)	17.72	15.18	8.77	—
S_{21} (API on film)	−32.2	−23.42	−9.93	—
W_a	128.40	137.18	150.67	—

Another important property is the thermoanalytical behaviour of a film which contains non-soluble components. The thermograms of different cast films just after their preparation are presented in Fig 8.

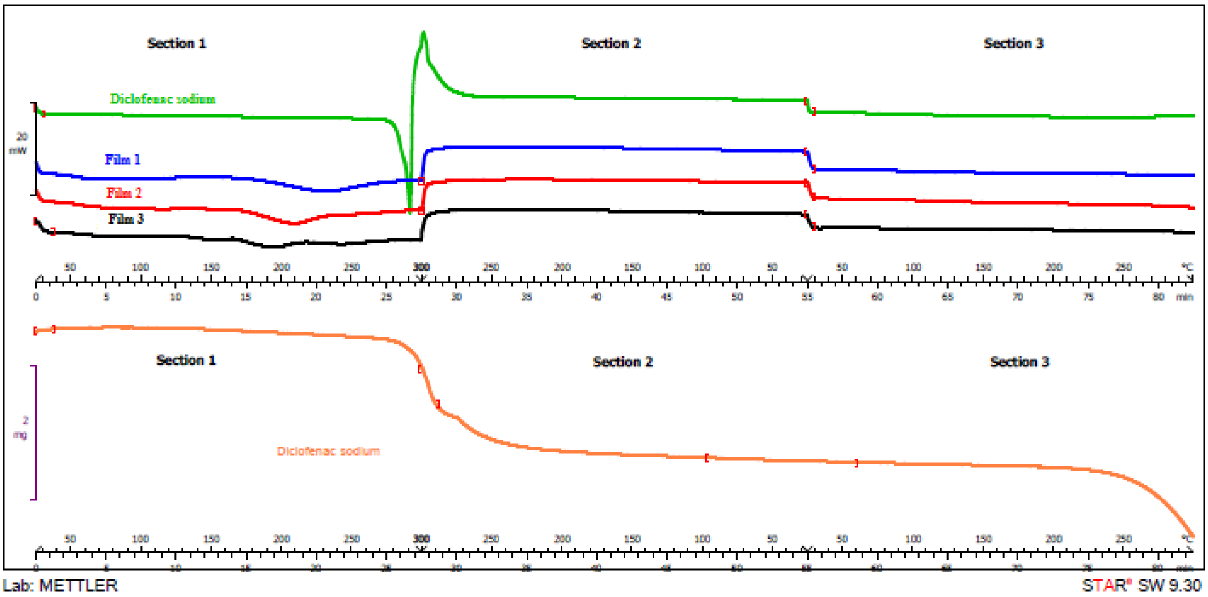

Fig. 8: Differential scanning calorimetry and thermogravimetric curves.

In the initial section (on the first heating), a glass transition can be seen for all the films (Table 10). The midpoint is shifted to a higher temperature level, and the range of the glass transition (onset-endpoint) is also increased in the cases of 1% and 5% API contents. The TG curves of the API showed that 6.1% of the API was lost in the first section (up to 300 °C) and 18% of the API was lost in the first two sections.

Table 10: Data on glass transition in the first section of the DSC curves

	API concentration		
Data	**0%**	**1%**	**5%**
Onset (°C)	49.98	51.85	45.75
Midpoint (°C)	56.16	59.11	63.5
Endpoint (°C)	60.21	64.26	73.13
Midpoint DIN* (°C)	55.05	58.04	59.06
Delta cp DIN (J/g K)	0.373	0.409	0.45

*DIN, Deutsche Industrie Normen.

In the third section (the reheating phase), a glass transition was detected for API content of 0% and 1%. These glass transition temperatures (Tg-s) were shifted and the range was also increased (Table 11). The material with an API content of 5% exhibited no glass transition.

Table 11: Data on glass transition in the last section of DSC

	API concentration	
Data	**0%**	**1%**
Onset (°C)	87.85	116.4
Midpoint (°C)	93.94	127.18
Endpoint (°C)	99.2	134.69
Midpoint DIN (°C)	93.43	125.52
Delta cp DIN (J/g K)	0.17	0.16

The reason may be that the API crystals disturb the internal structure of the film, leading to rearrangement of the macromolecules.

This internal structure and the free volume of the pores were tested by means of PALS. This measurement is very useful in the test of inner structure of polymers [77, 78]. It can be seen in Fig. 9 that the *o*-Ps lifetime is decreased by the presence of API in the films. Meanwhile, the formation intensity of *o*-Ps atoms remains, more or less, the same. The average size of free volume holes, according to Equation (1) (see at 3.2), is decreased from R=4.46Å to R=4.41Å. 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 (Fig. 9) suggested that the films containing the API are formed in a metastable structure.

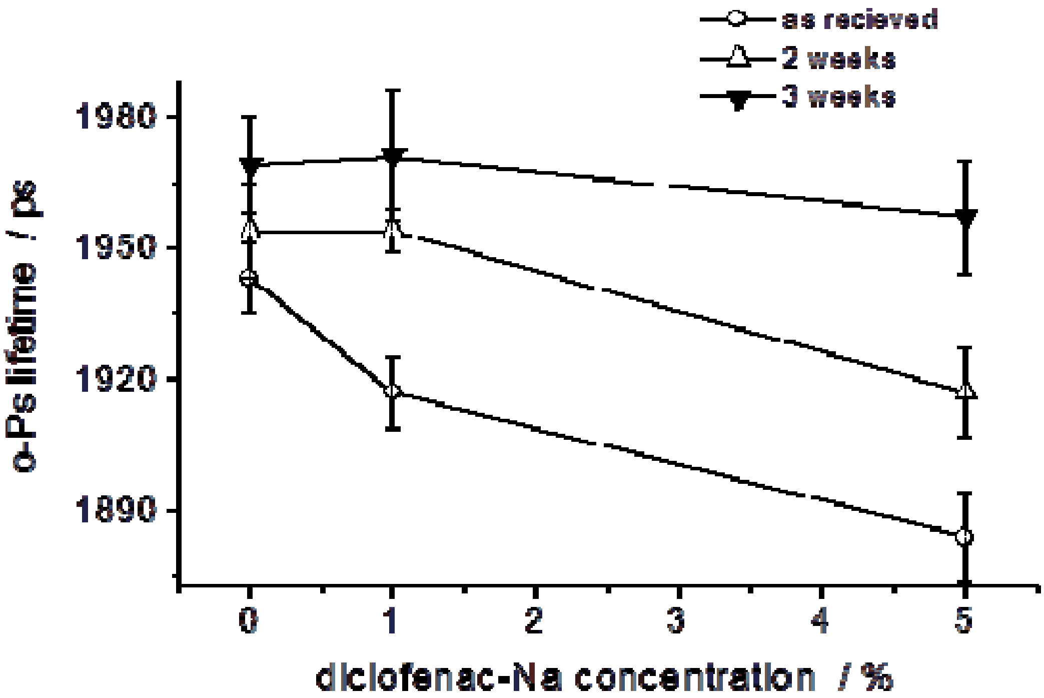

Figure 9: *o*-Ps lifetimes in films containing different amount of the API. The API distorts the original polymer structure but, as time goes by, the metastable structure relaxes and it is almost totally restored after three weeks of storage.

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 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.

These conclusions drawn from the average lifetimes were largely supported by the results obtained on the lifetime distributions (Figs. 10 and 11), but the picture was made clearer. Even the Film 1 displayed significant aging effects during the storage period. The extra peak first moved towards longer lifetimes and widened a little. It then moved backwards and sharpened again. The large peak around 2 ns exhibited opposite behaviour (Fig. 10). It should be noted that the lifetimes in Fig. 9 are the averages of the peaks of Fig. 10.

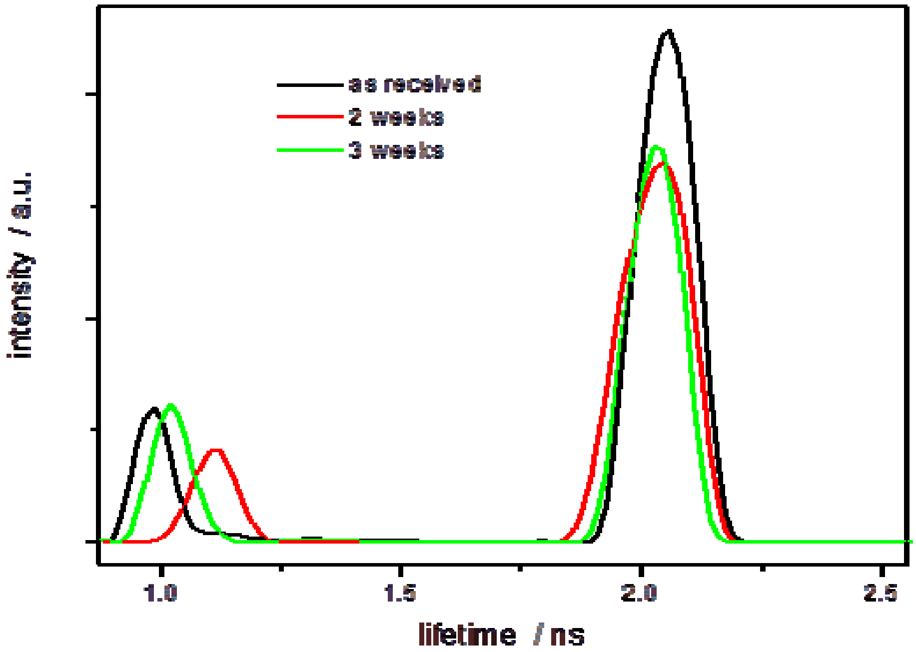

Figure 10: *o*-Ps lifetime distributions in Film 1. The extra peak (lifetime component) around 1 ns indicates a significant relaxation of polymeric chains during the storage period due to water uptake.

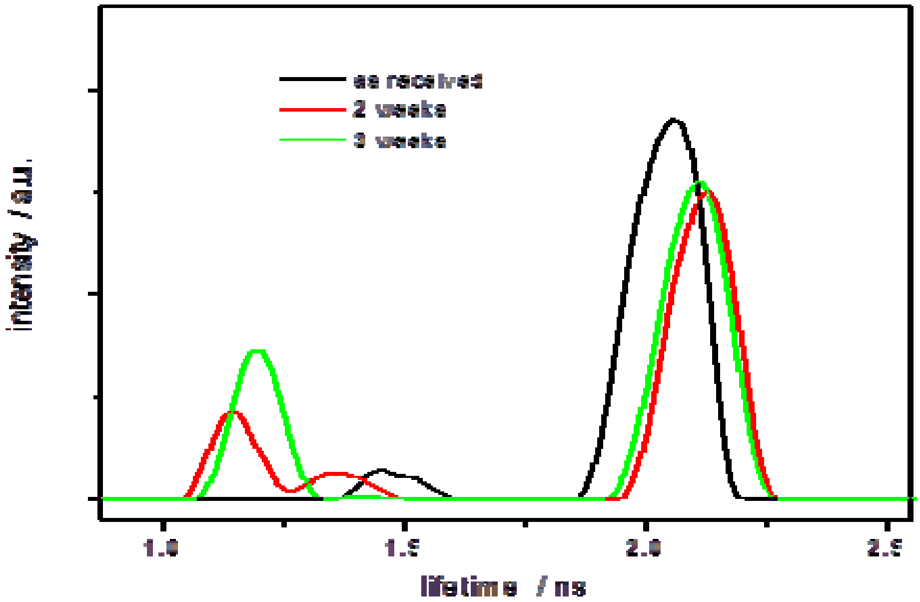

Figure 11: *o*-Ps lifetime distributions in Film 3 during the storage period. The relaxation is clearly shown by the peak(s) at around 1.25ns.

The shifting of peaks may indicate the effects of water uptake by the film [79]. Such water molecules initially destroyed the original polymeric structure, but a new structure was later formed, involving hydrogen-bonds between water molecules and the polymeric chains.

The structural changes were more dramatic for the films containing a large amount of the API (Fig. 11). The API distorted the structure of the Eudragit® L 30D-55 film significantly. The peaks were much wider indicating a more scattered distribution of the free-volume holes. Moreover, the extra peak was shifted considerably towards longer lifetimes and its intensity decreased. During storage, the two positronium states reacted differently to aging. The peak at 2 ns, indicative of *o*-Ps atoms situated in holes between polymeric chains, shifted a little towards longer lifetimes, demonstrating relaxation of the structure and on increase in size of the free-volume holes. This was most probably due to the plasticizing effect of water molecules absorbed from air.

On the other hand, the extra peak reacted strangely. It first split into two; the original peak then disappeared, and the new peak became higher. This alteration in the peaks indicates a process in which the original structure was transformed slowly to a new arrangement of molecules. As nothing similar happened in the pure film, the observed structural transformation was definitely connected with the API. We assume that the absorbed water molecules slowly changed the structure of diclofenac-Na (and/or that of the polymer) and a more stable arrangement of the molecules was formed, possibly involving first or second-order bonds between the API and the polymer. However, at the moment, we do not have more detailed knowledge concerning the nature of this transformation.

5.1.4. Discussion

All in all, it can be concluded that non-soluble particles influenced the mechanical strength of the free films. On the increase of the amount of API in the free films, SE and the polar part of SE, the polarity and the work of adhesion increased, whereas the spreading coefficient decreased. The DSC curves revealed that all the samples exhibited a glass transition in the first section, but in the third section, Film 3 had no glass transition in contrast with Films 1 and 2, which can be explained by the disturbing effect of the crystals in the film structure. Free-volume holes were defined by PALS, where the presence of the API resulted in a decrease in the size of the free volume holes. This decrease could be attributed to the effects of diclofenac on the structure of the films. The decrease subsequently vanished as the film absorbed water from the air and the structure relaxed because of the plasticizing effects of these water molecules. A metastable structure is formed during the preparation of Eudragit® L 30D-55 films containing diclofenac-Na. This metastable structure slowly relaxes during storage. Indications were observed that a structural (and/or chemical) transformation takes place around the API molecules.

6. Section 3

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 made by extrusion/spheronization using different types of apparatuses. (LII pellets were developed in the Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine University in Düsseldorf.) Last but not least the pellets were coated by coating liquids with and without containing API.

6.1. Section 3/I.

6.1.1. Materials

In the composition of the pellets, microcrystalline diclofenac sodium (Amoli Organics Pvt. Ltd., Gujarat, India) was used as an active pharmaceutical ingredient (API), MCC (Avicel PH 112, FMC Corp., USA) and ethyl acrylate-methyl methacrylate copolymer (Eudragit® NE 30D Evonik GmbH, Germany) as binder and matrix-forming agents, and purified water as granulation liquid.

6.1.2. Methods

The solid components of the powder mixtures (Table 12) were homogenized with a Turbula mixer (W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 minutes.

Table 12: Composition of powder mixtures

Components	Quantity (g)
Microcrystalline diclofenac sodium	50
Avicel PH 112	85

75 g of aqueous dispersion of polymer (Eudragit® NE 30D) was added manually to the mixture in a high-shear granulator with the same dosing speed as for purified water (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium) to prevent sticking in the pump. The mixture was moisturized further with a determined amount of purified water. The dosing speed and the amount of water were based on the data of the experimental design (Table 13). The dosing of water was carried out fractionally. The wet mass was kneaded with the following process parameters: impeller speed: 1500 rpm, chopper speed: 2000 rpm. The wet mass obtained was extruded by a mini screw (Caleva Ltd., Sturminster Newton, Dorset, UK) equipped with an axial screen with dies 1 mm in diameter and 4 mm in length, operating at 70 rpm. The jacked barrel of the extruder was cooled by water at 25 ± 2°C. Each extrudate was collected in a container before it was spheronized. About 40 g of extrudate was spheronized at a time, on a spheronizer 12 cm in diameter (Model-120, G.B. Caleva Ltd., Sturminster Newton, Dorset, UK) fitted with a cross-hatch grooved plate. The time and speed of the spheronization were determined by the experimental design (Table 13). The pellets were dried under the same conditions, at 40 ± 2°C for 24 h.

Table 13: Values of factors

Factor	Low (−)	Zero (0)	High (+)
Quantity of purified water (X_1)	60	70	80
Dosing speed (X_2)	3	5	7
Speed of spheronization (X_3)	750	875	1000
Duration of spheronization (X_4)	10	15	20

6.1.2.1. Factorial design

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 16 experimental set-ups supplemented with a central point are indicated in Table 14. The experiments were performed in randomized sequence, so as to eliminate systematic errors.

Table 14: Designation of samples

	Quantity of Purified water (ml)	Dosing speed (ml/min)	Speed of spheronization (rpm)	Duration of Spheronization (min)
Pellet 1	60	3	750	10
Pellet 2	80	3	750	10
Pellet 3	60	7	750	10
Pellet 4	80	7	750	10
Pellet 5	60	3	1000	10
Pellet 6	80	3	1000	10
Pellet 7	60	7	1000	10
Pellet 8	80	7	1000	10
Pellet 9	60	3	750	20
Pellet 10	80	3	750	20
Pellet 11	60	7	750	20
Pellet 12	80	7	750	20
Pellet 13	60	3	1000	20
Pellet 14	80	3	1000	20
Pellet 15	60	7	1000	20
Pellet 16	80	7	1000	20
Pellet 17	70	5	875	15

The following approach, containing the interactions of the factors, was used to determine the response surface and the relative effects of the factors (b):

$$y=b_0+b_1X_1+b_2X_2+b_3X_3+b_4X_4+b_{12}X_1X_2+b_{13}X_1X_3+b_{23}X_2X_3+b_{14}X_1X_4+b_{24}X_2X_4+ \\ b_{34}X_3X_4+ b_{123}X_1X_2X_3+b_{234}X_2X_3X_4+b_{124}X_1X_2X_4+b_{134}X_1X_3X_4$$

Statistica for Windows 8.1 AGA software (StatSoft, Inc. Tulsa, USA) was used for the calculations. During the mathematical evaluations, the confidence interval was 95%, i.e. the differences were significant if $p < 0.05$.

6.1.2.2. Morphological study

The particle size and the shape of the pellet surface were studied with a stereomicroscope (Zeiss Stemi 2000-C, Carl Zeiss GmbH, Vienna, Austria). A Quantimet 500 (Q500MC) image processing and analysis system (Leica Cambridge Ltd., Cambridge, UK) was used. The aspect ratio was utilized for the evaluation of the shape of the particles. 500 pellets of each sample were checked.

6.1.2.3. Mechanical properties of the pellets

The breaking hardness was tested for pellets with diameters measuring between 1000 and 1250 μm. The strength tester and the software were developed in our institute (same as used by films but different specimen holder and stamp). The measurement range was 0–200 N, the speed of the stamp was 20 mm/min, and the output was 0–5 V. The sensor was a Unicell force measuring instrument, calibrated with the C9B 200N cell.

6.1.2.4. Dissolution tests

Pellets (160 mg) were placed into the basket of a dissolution tester (Erweka DT 700, Heusenstamm, Germany). The dissolution medium consisted of phosphate buffer (pH 6.8), kept at 37.0 ± 0.5°C for 4 hours. The rotational speed of the baskets was set at 100 rpm. The dissolution system was combined with an automatic sampling station. Samples of 5 ml were withdrawn from the phosphate buffer medium at 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Absorbance was measured spectrophotometrically (Unicam Heλios α, Spectronic Unicam, Cambridge, UK) at λ_{max} = 276 nm. Three parallel tests of dissolution were performed.

6.1.3. Results

The present work was focused on optimization of the shape and mechanical properties of pellets prepared by extrusion-spheronization. Table 15 displays the aspect ratios and breaking hardness of the different samples.

Table 15: Aspect ratio and breaking hardness

	Aspect ratio	**Breaking hardness**
Pellet 1	3	41.78±8.27
Pellet 2	-	-
Pellet 3	3	53,13±12.36
Pellet 4	3	32.74±6.15
Pellet 5	3	48.03±10.48
Pellet 6	-	-
Pellet 7	3	45.57±10.54
Pellet 8	1.142±0.08	44.38±6.93
Pellet 9	3	47.41±13.84
Pellet 10	-	-
Pellet 11	1.637±0.35	53.17±8.88
Pellet 12	1.183±0.11	32.79±2.69
Pellet 13	3	49.91±8.32
Pellet 14	-	-
Pellet 15	1.463±0.29	45.82±8.16
Pellet 16*	1.082±0.04	37.55±5.24
Pellet 17	3	47.83±9.17

*The best product

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. For all the samples, the deformation process (Fig. 13) could be divided into three phases: a short elastic part (1), followed by a plastoelastic phase (2), and finally an elastic section peaking (3) at the breaking point.

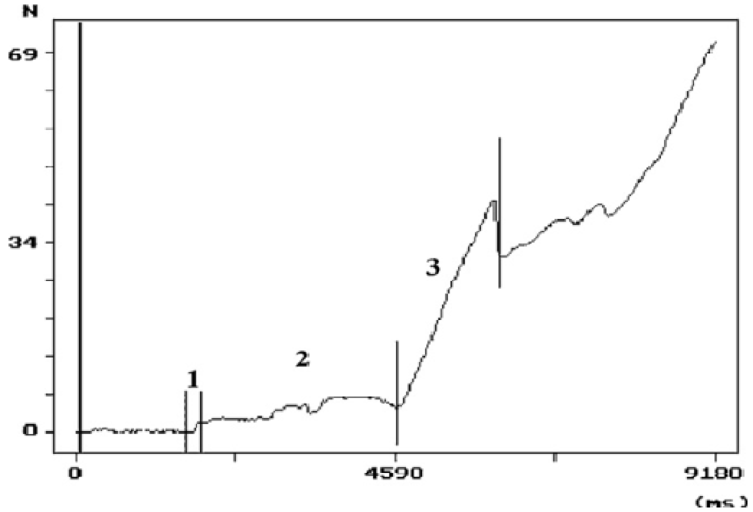

Fig. 13: Curve of pellet deformation

The similarity of the curves for the various samples suggests that the mechanism of deformation of the pellets is primarily based on the composition of the product and is only minimally affected by the parameters of the production process. Nevertheless, the breaking hardness of the products is significantly influenced by the process parameters (Table 16). The significant factors and linear interactions are highlighted in red; the level of significance was determined in *t*-tests.

Table 16: Effects of the parameters on the breaking hardness

Var.:Breaking hardness, $R^2 = 0.98308$

	Effect	**Std. err.**	**t(5)**	***p***	**Coeff.**
Mean/Interc.	33.27	1.17	28.5153	0.000001	33.27
(1) quantity of water	−29.67	2.33	−12.7159	0.000053	−14.84
(2) dosing speed	19.75	2.33	8.4654	0.000378	9.88
(3) speed of spheronization	1.28	2.33	0.5486	0.606891	0.64
(4)duration of spheronization	0.13	2.33	0.0546	0.958539	0.06
1 by 2	17.11	2.33	7.3340	0.000739	8.5
1 by 3	2.82	2.33	1.2086	0.280855	1.41
1 by 4	−1.82	2.33	−0.7811	0.470103	−0.91
2 by 3	−0.91	2.33	−0.3889	0.713337	−0.45
2 by 4	−1.75	2.33	−0.7500	0.487020	−0.88
3 by 4	−1.30	2.33	−0.5582	0.600766	−0.65

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, because the water acts as a plasticizing agent in the mixtures. 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. When a lower liquid feeding rate is used, the water can spread on the surface even of the small particles and can form an incompressible barrier during extrusion. This is the reason why compositions containing a high amount of water added at a low dosing speed cannot be extruded. At higher feeding rates, this effect is of less importance (Fig. 14): because of the shorter kneading time dry aggregates remain in the wet mass, which provides sufficient bonding of the particles during extrusion.

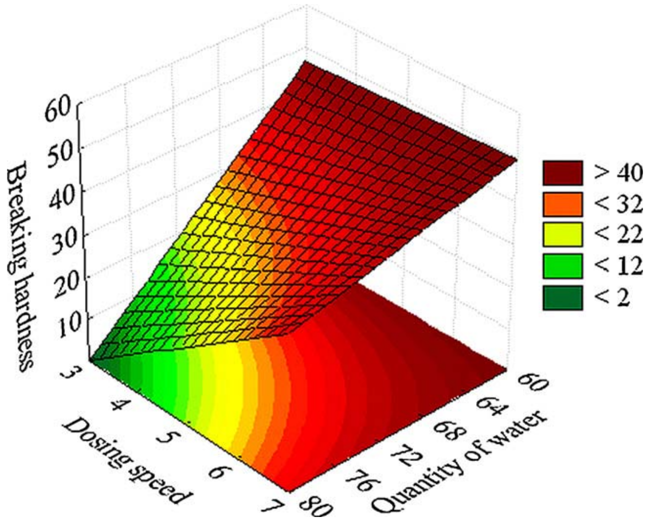

Fig. 14: Effects of dosing speed and quantity of water on the breaking hardness of the pellets.

This is a possible explanation of why the feeding rate has a positive effect on the mechanical properties of the pellets. This advantageous effect could be seen not only in the breaking hardness, but also in the deformability of the extrudates. Besides the duration of spheronization, the dosing speed and the linear interaction of the two factors exert significant effects on the shape of the pellets (Table 17).

Table 17: Effects of the parameters on the shape of pellets

Var.: Aspect ratio $R^2 = 0.91254$

	Effect	**Std. Err.**	**t(5)**	***p***	**Coeff.**
Mean/Interc.	2.47	0.113	23.44626	0.000003	2.47
(1) quantity of water	−0.34	0.21	−1.59822	0.170887	0.17
(2) dosing speed	−1.06	0.21	−5.04035	0.003966	0.53
(3) speed of spheronization	−0.27	0.215	−1.26587	0.261334	0.13
(4) duration of spheronization	−0.60	0.21	−2.83501	0.036459	0.30
1 by 2	−0.34	0.21	−1.59822	0.170887	0.17
1 by 3	−0.22	0.21	−1.05935	0.337912	0.11
1 by 4	0.13	0.21	0.60712	0.570282	0.06
2 by 3	−0.27	0.21	−1.26587	0.261334	0.13
2 by 4	−0.60	0.21	−2.83501	0.036459	0.30
3 by 4	0.20	0.21	0.93946	0.390624	0.10

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 (Fig. 15).

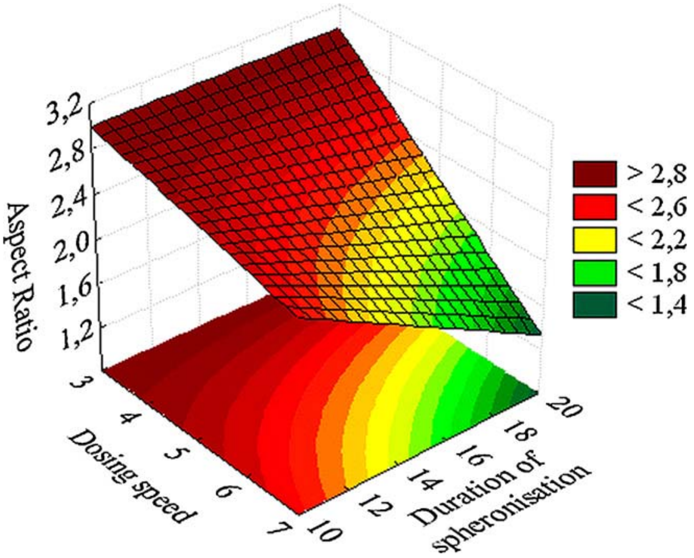

Fig. 15: Effects of dosing speed and duration of spheronization on the aspect ratio of the pellets.

The effects of the speed of spheronization and the quantity of water were not significant, but still considerable, which is important, because the data in Table 15 show that the aspect ratios of many samples were far from the ideal value.

The aspect ratio was close to 1 in the case of Pellet 12, but was best for Pellet 16. It can also be seen, that the breaking hardness of this sample was very good. It is known that the shape can modify the breaking hardness of different systems (mainly for tablets) [80, 81].

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. To decrease the rate of aggregation the decreasing of the water quantity was necessary. Nevertheless, this will have a negative effect on the aspect ratio of pellets. 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. The calculations based on equation of response surface showed that the further change of the conditions of spheronization will be not necessary, so they were kept in +1 level.

On the basis of these considerations a new combination of factors (Pellet 18) was applied (Table 18), where we achieved matrix pellets with optimized characteristics (aspect ratio: 1.083±0.04, breaking hardness: 38.18N±4.16).

Table 18: Manufacturing factors of the product.

	Quantity of purified water (ml)	**Dosing speed (ml/min)**	**Speed of spheronization (rpm)**	**Duration of spheronization (min)**
Pellet 18	62	9	1000	20

In this case too, the impeller torque increased at the end of the process, but not as significantly as for Pellet 16; and no large aggregates were formed. The SEM picture reveals that the surface of Pellet 18 is smooth, without pores (Fig. 16).

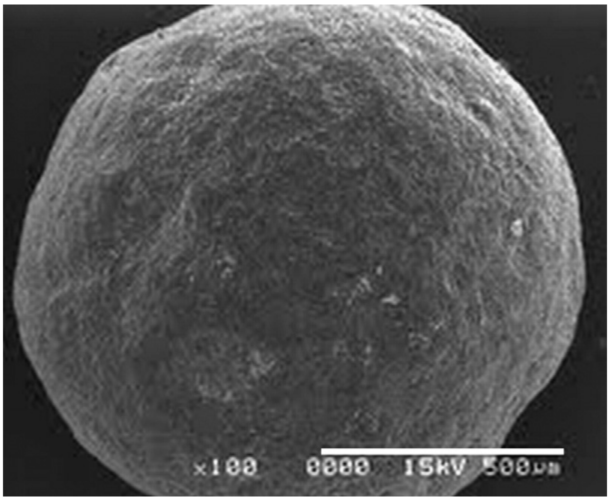

Fig. 16: Surface of Pellet 18 (SEM)

The cross-section picture demonstrates the compact texture (Fig, 17/A), and at higher magnification it is clear that the particles formed a matrix system (Fig. 17/B).

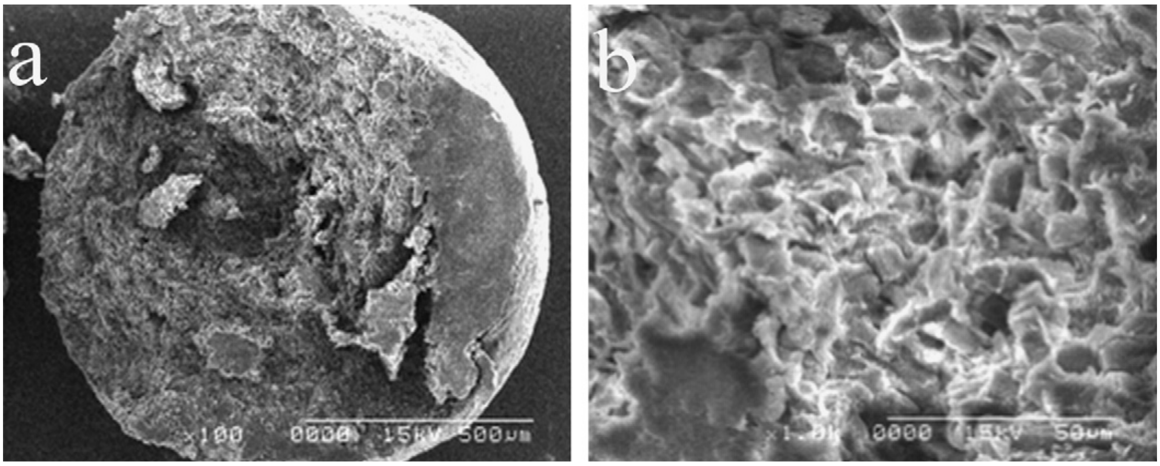

Fig. 17: Cross-section of Pellet 18 (SEM); magn. 100× (A), 1000× (B).

The physical parameters indicated that this sample was suitable for dissolution studies. 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 (Fig. 18).

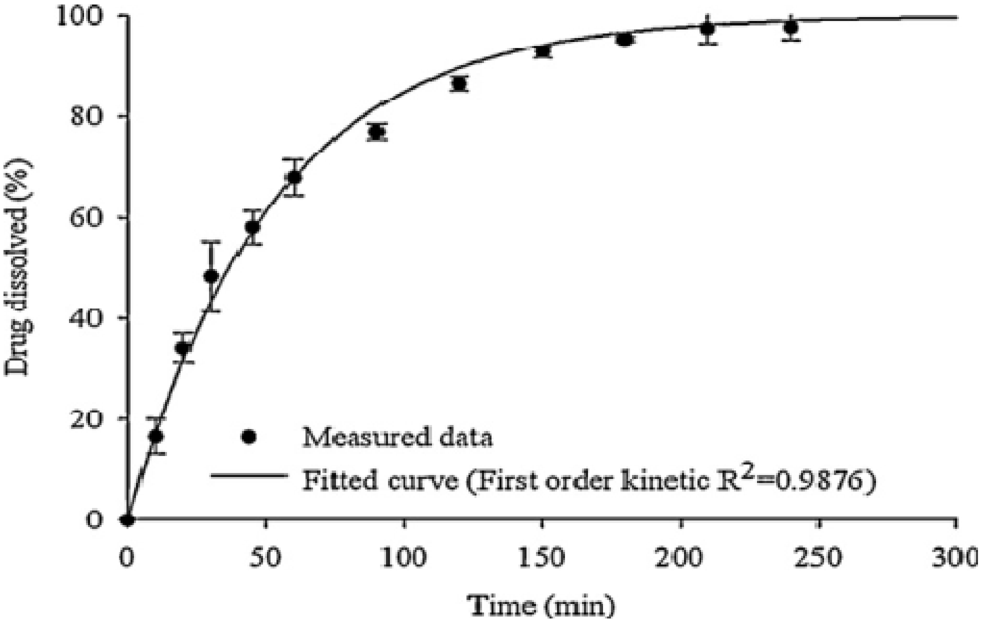

Fig. 18: Dissolution rate of the drug of Pellet 18.

6.1.4. Discussion

It can be 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 (pH = 6.8). This means that this product may be used as a delayed release dosage form.

6.2. Section 3/II

6.2.1. Materials

Composition was the same as for laboratory scale I. 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 composition can be seen in Table 19.

Table 19: Composition of powder mixture for LII.

Components	Quantity
1. Microcrystalline Diclofenac Sodium	120 g
2. Avicel PH 112	204 g
3. Eudragit® NE 30D	180 g
4. Purified Water	165 g

6.2.2. Methods

The weighed powders (1 and 2) were transferred into a laboratory-scale blender (LM40, Bohle, Ennigerloh, Germany) and blended for 30 min at 35 rpm. The dry powders were then wetted first with Eudragit® NE 30D (3) dispersion and after that with purified water (4) using a high shear mixer (Mini-MGT, Bayer, Leverkusen, Germany) at 400 rpm and a peristaltic pump (Miniplus3, Beckman, Germany) at 9 ml/min. The wetted mass was supplied to a flat die press 14-175 (Amandus Kahl, Germany) at a feeding screw rate of 180 rpm and extruded at a roller speed of 30 rpm through a flat screen with dies of 1 mm in diameter. The distance between the screen and knife was adjusted to 3 mm.

Collected extrudate batches of approximately 300 g were transferred into a spheronizer (RM 300, Schlueter, Neustadt/Ruebenberge, Germany) fitted with a cross-hatched rotor plate of 300 mm in diameter and were spheronised for 8 min at a spheronization speed of 1000 rpm and a temperature of 25°C. The resulting pellets were then transferred to a fluid bed drier (GPCG 1.1, Glatt, Dresden, Germany) and dried for 20 minutes at 60°C with an air volume of 130 m^3/h.

These pellets were studied morphologically and mechanically by the methods described in chapter 6.1. Dissolution tests were also carried out under the same circumstances as by laboratory scale I.

Tensile strength of pellets was also determined with the following equation (Eq. (9)) [82]:

$$\sigma_s = \frac{0{,}4F}{\pi R^2} \qquad (9)$$

where σ_s =tensile strength

F = breaking force

R = radius of pellets

6.2.3. Results

Table 20 shows that aspect ratio is quite the same in both, but the size became smaller in case of LII.

Table 20: Shape parameters and mechanical properties of pellets (mean ±- sd, n=500)

	Length (mm)	**Breadth (mm)**	**Aspect Ratio**	**Breaking Hardness (N)**	**Tensile strength (N/mm^2)**
LI.	1.33±0.11	1.23±0.09	1.08±0.04	38.18±4.16	11.87
LII.	1.15±0.14	1.05±0.12	1.1±0.08	25.84±3.16	10.87

According to previous results in our institute [83, 84] breaking hardness (Table 20) of both batches was high enough for further processing, e.g. coating. The pellets were not deformed or abraded due to mechanical stress. 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 results show that in this case the size of pellets is crucial. The values in case of LII are about the half of the values of LI. These results prove that the textures are not the same. LI's texture is more compact, the inner forces are bigger than in case of LII.

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 (Fig. 19.).

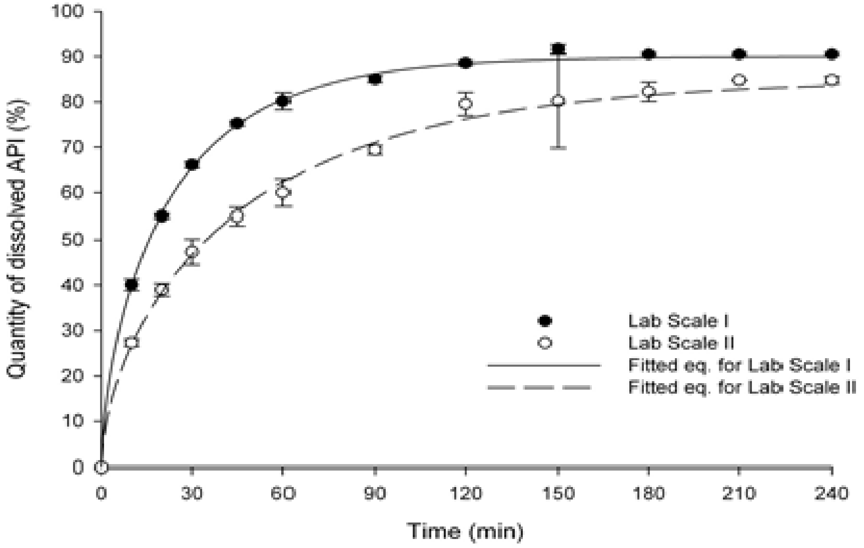

Fig 19: Dissolution of pellets

The results of dissolution studies shows, that the drug release from the different samples follows the same kinetic, which can be described with a modified Noyes-Whitney equation (Eq. (10)). After trying other models (Higuchi, Hixon-Crowell, RRSBW, etc.) the Noyes-Whitney equation indicated the best fitting that could be improved by the modification of this equation.

$$M = M_{\infty} (1^{-e-kt})c \tag{10}$$

Where where *M* is the dissolved amount of API at given time, M_{∞} is the dissolved amount at infinite time, *k* is the dissolution rate constant, and *c* is a constant which is related to the structure change of the matrix during dissolution. The calculated data are displayed in Table 21.

Table 21: Calculated values of the kinetic profile

	K	**c**
LI.	0.0295	0.5958
LII.	0.0147	0.5811

The modification of the Noyes-Whitney equation was necessary, because the original theory assumed that the matrix is not affected at all during the dissolution. Meanwhile, the Eudragit® NE 30D shows a pH independent swelling in aqueous media, which is resulted in burst effect in the first stages of drug release. The value of the swelling constant is statistically the same, which suggest that this effect is generally based on the materials properties and less affected by the process parameters. Nevertheless, despite of the same burst effect, 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. It means that the LII. process should be examined better in this matrix pellet composition to ensure the properties of the original LI pellets.

6.2.4 Discussion

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.

6.3 Section 3/III.

6.3.1 Materials and methods

Matrix pellets produced in Section 3/I-II. were coated in a Strea-1 (Niro Aeromatic, Bubendorf, Switzerland) fluid bed Wurster chamber. Coating fluids containing 0 and 4.375% of API were prepared as described in Section II. (Atomization of the coating fluid containing 5% of API was not possible with the given nozzle (diameter of 1 mm)). The coating liquids contained Eudragit L 30D as a polymer that forms an enterosolvent film on the surface of the pellets to protect the stomach from the local side effect of the API (diclofenac sodium). That is why were tested these compositions in Section 2. The liquid was layered onto the surface of preheated pellets at 40°C. The coating conditions were different in the two batches (Table 22).

Table 22: Coating conditions

	Coating liquid without API (Coating 1)	**Coating liquid with API (Coating 2)**
Nozzle diameter (mm)	1	1
Peristaltic pump speed (rpm)	5	3
Fan capacity	5	6
Air volume (m^3/h)	75	120
Outlet temperature (°C)	36	38

As a last step the coated pellets were dried at 40° C for 15 minutes. Coating 2 was used only in case of LII because the aim was to accelerate the starting rate of dissolution. The material loss was about 0.12% in case of Coating 1 and 18% in case of Coating 2.

6.3.2. Dissolution studies

Dissolution studies were carried out according to the Ph. Eur. standards with a rotating basket (Erweka DT 700, Erweka GmbH, Heusenstramm, Germany), in 1000 ml of simulated gastric acid at 100 rpm at 37 °C for 2 h, then after draining the vessel of the acid it was replaced with 1000 ml of phosphate buffer pH=6.8 and the dissolution measured at the same parameters as above. Samples were taken of the phosphate buffer at 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes. Concentration was measured with a spectrophotometer (Unicam Heλiosα, Thermo Fisher Scientific Inc., Waltham, USA) at 237 nm.

6.3.3. Results

Dissolution curves of both pellets coated by Coating 1 can be seen in Figure 20. Both curves are similar, after about 150 minutes the whole amount of API was dissolved.

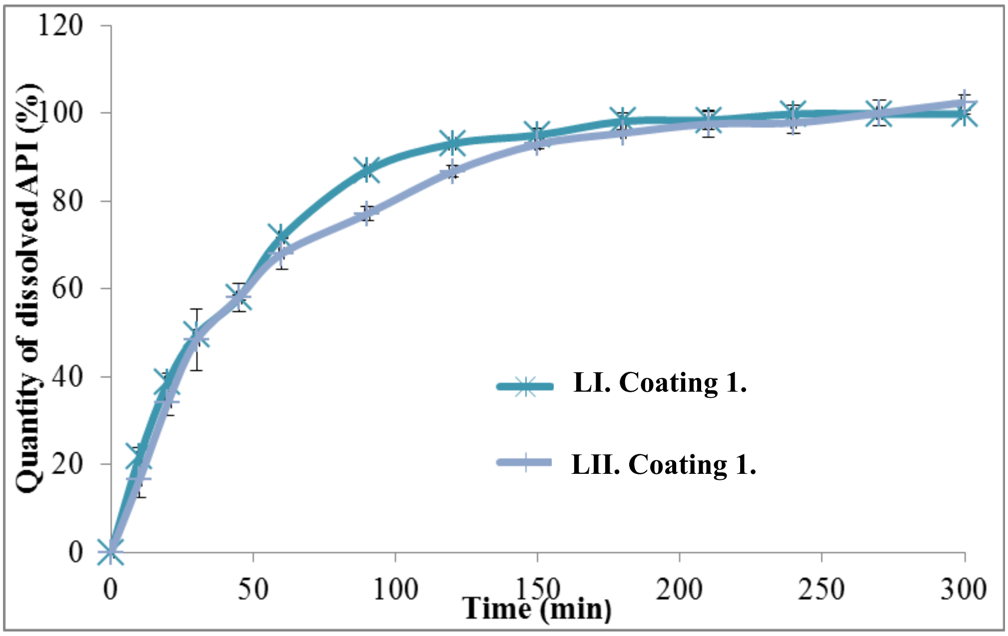

Fig 20: Dissolution of both pellets coated by Coating 1

Dissolution of LII pellets coated by Coating1 and 2 was also compared (Fig 21.). 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.

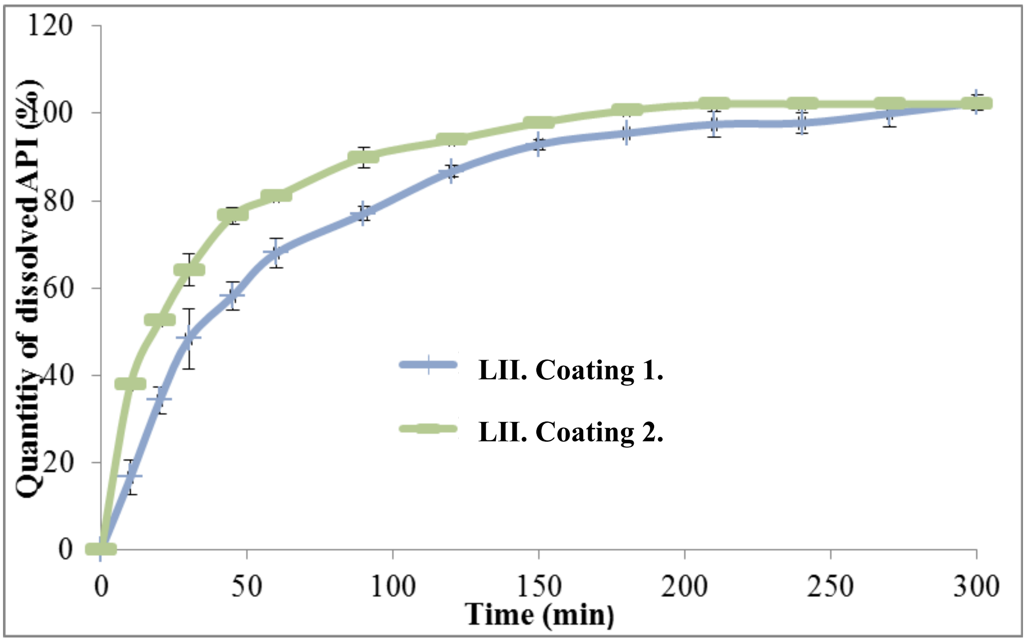

Fig. 21: Dissolution of LII. pellets coated by Coating1 and 2

6.3.4. Discussion

It can be concluded, that the use of micronized API in this coating liquid composition and coating process is possible. The particle size of the API is crucial; bigger particles can block the nozzle and is inevitable that the film formed contains no bigger particles that can lead to flaws in the film layer. The aim was to study whether certain amount of API in the coating liquid accelerates the starting rate of dissolution and increases the rise in the concentration of the dissolved API. 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.

7 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 drug 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 as well.

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

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APPENDIX

PUBLICATIONS RELATED TO THE THESIS

I

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Short communication

Rapid method to study the sedimentation of a pigment suspension prepared for coating fluids

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Abstract

Film coating fluids commonly contain a pigment suspension. The sedimentation of insoluble particles in the coating suspension is one of the main problems during the formulation of the coating fluid. The aims of this work were to investigate the suitability of an energy-dispersive X-ray fluorescence analyser for rapid measurement of the sedimentation of titanium dioxide in aqueous suspensions. The suspensions were produced with a high-speed Ultra-Turrax. The process factors evaluated were the stirring rate, time and volume, and the process of sedimentation of the pigment. The enrichment of the pigment at the bottom of the sample holder was followed by means of the very rapid method of energy-dispersive X-ray fluorescence analysis. It can be concluded that the sedimentation of the particles is described by the Weibull equation. With an appropriate combination of the factors, a threefold increase in the sedimentation time was achieved. The mathematically based information (sedimentation time, kinetics of sedimentation, etc.) is essential for an exact evaluation of the preparation of the coating fluid. The understanding of the process through use of this test method leads to the ability to identify the critical control points of film coating.

Keywords: Energy-dispersive X-ray fluorescence analysis; Factorial design; High-shear mixer; Pigment suspension; Sedimentation; Titanium dioxide

1. Introduction

Film-forming polymers in aqueous dispersions are increasingly used during the production of coated solid dosage forms [1]. Various types of polymers can be used to form aqueous dispersions, and numerous water-soluble and insoluble additives are applied to change the properties of the films and to increase the processibility of these liquids [2,3]. Insoluble pigments (e.g. iron oxide, titanium dioxide, etc.) are applied to ensure the appropriate appearance of the coated product [4]. They can modify the properties of the film formed [5,6] and thus their homogeneous distribution is indispensable.

The suggested mixing sequence for the preparation of a coating liquid containing insoluble particles is very important. According to a manufacturer of dispersions, the first step is the preparation of the pigment suspension [7]. In this case, the intensive homogenization of the materials (glidants, pigments, plasticizers and other excipients) in water must be performed with a high-speed mixing apparatus. After this, the freshly prepared homogeneous pigment suspension must be gently mixed with the polymer dispersion. High-speed mixing can cause precipitation of the polymers and foaming, and this apparatus can therefore not be used in this step [8,9]. The even distribution of the insoluble particles in the pigment suspension is very important because gentle mixing cannot break pigment aggregates.

The main problem that can arise during formulation of the coating fluid is the sedimentation of the pigments, which can cause an uneven coating layer and/or difficulties in the coating process. Various additives are applied to eliminate this problem for orally or topically used suspensions [10]. These materials are not recommended for pigment suspensions prepared for coating dispersions because of the possibility of changes in the properties of the films.

Despite the importance of sedimentation as a critical control point in the formulation of the coated product, this has been relatively neglected to date. The difficulty in the rapid determination of the homogeneity of the pigment is its sedimentation during the sampling. The main objective of our project was to establish an exact quick method with which to evaluate the sedimentation of pigment suspensions. The aims of this work were

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to investigate the suitability of an energy-dispersive X-ray fluorescence analyser for rapid measurement of the sedimentation of pigments and to determine the parameters that can be applied for the preparation of pigment suspensions. The technique is suitable for direct measurement of the element component of a drug [11].

When a material is irradiated by the beam from an X-ray tube, its constituent atoms are excited. This causes them to emit X-rays as fluorescence. Each element in the sample emits its own uniquely characteristic fluorescent radiation, with an intensity directly related to the concentration of that element in the material. This phenomenon is the basis of X-ray fluorescence spectrometry.

Titanium dioxide was applied as an insoluble additive in our study. For an appropriate light protective effect, the even distribution of these particles is necessary [12]. An Ultra-Turrax mixer was used to disperse the powder in water. In consequence of their unwanted effects (modification of the permeability, solubility and stability [13–15]), other additives (suspending and viscosity-increasing agents), were not used. The titanium content of the pigment suspension and the enrichment of the pigment at the bottom of the sample holder were measured with an energy-dispersive X-ray fluorescence analyser. The kinetics of sedimentation of the pigment suspension was followed. Several technological aspects were evaluated with the aim of decreasing the sedimentation. The mathematically determined effects of different factors were compared by means of a factorial design. This information is very useful for the application of process analytical technology (PAT). Since gaining a deep understanding of the manufacturing process is at the heart of PAT [16–18].

2. Experimental

2.1. Materials

Commercial titanium dioxide (Merck GmbH, Darmstadt, Germany) was used, where the particles form aggregates. It was dispersed in distilled water at a concentration of 10%.

2.2. Factorial design

The fluid was stirred in glass beakers with identical dimensions (7.7 cm in diameter) with an Ultra-Turrax mixer (IKA Ultra-Turrax T25 basic, IKA-Werke GmbH & Co. Kg, Staufen, Germany). The diameter of the turbine was 1.85 cm in diameter. The turbine of mixer was located in the midst of container. A 2^3 full factorial design was applied for different mixings; the factors were the stirring rate (X_1), the stirring time (X_2) and the volume (X_3), with the levels to be seen in Table 1. The eight experimental set-ups were supplemented with a central point.

Table 1
Levels of factors

Factor	Low (−)	Zero (0)	High (+)
X_1	9500 rpm	13500 rpm	17500 rpm
X_2	5 min	7.5 min	10 min
X_3	100 ml	150 ml	200 ml

Statistica for Windows 6.1 AGA (StatSoft, Inc. Tulsa, USA) software was applied to determine the effects of the factors. The following linear approach was applied to determine the surface of the response:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

The b_0 (intercept) is the mean for y value of nine samples.

2.3. Determination of titanium dioxide content

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 (PW 4025/00, Minipal Philips, Almelo). This compact table-top instrument can be used to measure the elemental range from sodium (Na) to uranium (U), in the concentration range from ppm to 100%, and it ensures very rapid and facile data acquisition.

The conditions applied during the measurements were 8 kV, 120 μA and an air purge with a kapton filter. The samples were measured for 20 s. The linearity of calibration was checked between the titanium content of 4–12% (6.6–20% of titanium dioxide). The R^2 was 0.9827. The accuracy of the method was checked with liquids containing a certain amount of titanium dioxide. The difference between calculated and measured concentration was not significant (t-test, $p < 0.05$). The pigment suspensions poured into the sample holder and they were tested directly without withdrawing. Three parallel tests were performed.

The sedimentation curves were constructed from the measured data. The maximum in the sedimentations when the concentration reached the highest level, was taken as 100%. The other results were calculated from the concentration ratios. The fitting revealed that these curves can be described by the Weibull model [19]. A non-linear fitting approach with the following equation was applied:

$$M = M_0 \left\{ 1 - \exp\left[-\frac{(t-T)^{\beta}}{a} \right] \right\}$$

where M is the percentage sedimentation up to time t, M_0 the maximum percentage sedimentation, T the delay time, β the shape parameter, and a is the scale parameter.

The characteristic sedimentation time ($t_{63.2\%}$), i.e. the time necessary to reach 63.2% of the maximum enrichment of titanium dioxide, was determined from the curve.

3. Results and discussion

The enrichment of titanium dioxide at the bottom of the sample holder was readily measured with this very rapid test method. It can be seen from the sedimentation profile that there were no

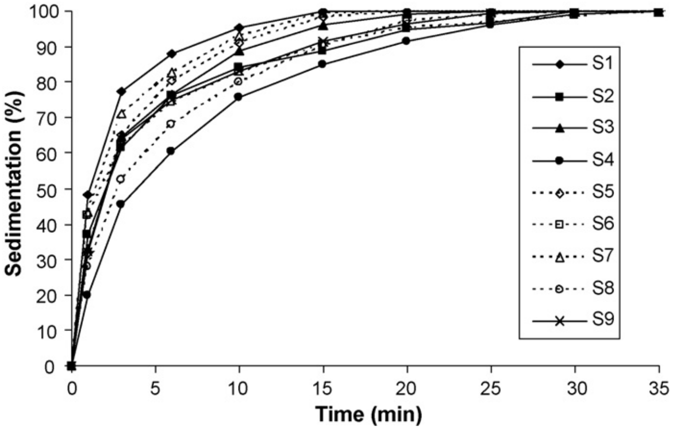

Fig. 1. Sedimentation curves for pigment suspensions.

fundamental differences between the characteristics of the sedimentation curves, but the courses were not identical, e.g. the maximum sedimentation was reached at 15 min for S1 and at 35 min for S4 (Fig. 1).

The fittings were very good, because the R^2 values were higher than 0.99. The results derived from the fitting were different for the different samples (Table 2). Since the characteristic sedimentation time of the sample with a low mixing rate and a low mixing time was very short, the addition of this suspension to the polymer dispersion must be very quick. Accordingly, increase of this time is inevitable. An appropriate combination of the factors can cause a threefold increase in the sedimentation time (see Section 3 for S1 and S4). The values of the shape parameters (β) are less than 1, and thus the curves are saturation curves with a fast initial increase.

The values of the scale parameter (a) indicate the speed of increasing of the curve. The higher the value is, the slower the sedimentation is. The highest one was detected for S4 (just as it was seen at the sedimentation time).

The characteristic sedimentation times were compared by means of the factorial design. The linear estimation with the interactions was very good ($R = 0.9998$). Table 3 presents the ranked order of the factors. The stirring rate, the time and the interaction of these factors were significant in the 99% confidence interval. The higher are the values of these factors, the longer is the sedimentation time. Change of the stirring rate can cause a more than twofold increase in the sedimentation time relative to the increase caused by change of the stirring time. The sample volume on this laboratory scale was not a significant factor, but it can be concluded that increase of the volume decreases the sedimentation time. This statement is indicated by the negative sign of the coefficients for volume and the two-factor interaction containing the mixing volume.

Table 2
Kinetic study parameters

Sample	X_1	X_2	X_3	$t_{63.2\%}$ (s)	Corr.	a	β
S1	−	−	−	2.03	0.9968	1.74	0.9613
S2	+	−	−	4.28	0.9957	3.79	0.9068
S3	−	+	−	2.90	0.9969	2.75	0.9289
S4	+	+	−	6.69	0.9955	4.42	0.8975
S5	−	−	+	2.89	0.9967	2.45	0.9398
S6	+	−	+	4.29	0.9952	3.61	0.9014
S7	−	+	+	2.42	0.9972	2.13	0.9468
S8	+	+	+	6.03	0.9955	3.94	0.9102
S9	0	0	0	3.92	0.9971	3.38	0.9130

Table 3
Factorial design parameters

Factors	Coefficients
b_0	3.9388*
b_1	1.3813*
b_2	0.5688*
b_{12}	0.4687*
b_{23}	−0.2513
b_{13}	−0.1288
b_{123}	0.0837
b_3	−0.0338

* Significant ($p < 0.01$).

The three-factor interaction was less relevant. The positive sign in the equation of the response surface indicates a slight increase in the sedimentation time.

4. Conclusions

It may be concluded that the change in the concentration of titanium dioxide can be detected by energy-dispersive X-ray fluorescence analysis. In a pigment suspension without additives, the sedimentation is a very quick process, which can be described by the Weibull model. The sedimentation of this pigment suspension can be changed via the appropriate parameters of the Ultra-Turrax mixer. The application of this rapid test method and the determination of the characteristic sedimentation time allowed comparison of the effects of different technological parameters.

This information is indispensable for a more accurate knowledge of the preparation of the coating fluid and for detection of the critical control point of coating. Accordingly, their precise control can promote the formulation of a coating fluid and the occurrence of the coating process with less chance of disturbing effects.

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II

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Study of the Effect of an Antifoaming Agent on the Evaporation of the Components During the Stirring of a Coating Dispersion Containing a Volatile Agent

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The main objective of this work was to evaluate the evaporation of coating liquids containing a volatile component (ethanol) and an aqueous polymer dispersion under well-controlled circumstances. The influence of different concentrations of a polydimethylsiloxane type antifoaming agent was studied. In consequence of to its low interfacial tension, it can form a layer on the surface of a liquid, and the effect of this was studied by determination of the quantity of the stirred liquid that was evaporated. The effects of different operational factors were compared by means of factorial designs. It was conluded that 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 Dimeticon decreased the extent of evaporation, but not significantly. Thus, the alterations in the effects of the operational factors were not very substantial either. It may be stated that this antifoaming agent 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. This information helps towards the design of an appropriate stirring device, because our results indicate that open systems are not adequate and it is known that hermetically closed tanks make atomization impossible. Hence, determination of the critical control points of coatings with a liquid containing a volatile component cannot be avoided because the vapour of such materials can be very dangerous.

Keywords Dimeticon, ethanol, aqueous polymer dispersion, evaporation, factorial design

INTRODUCTION

Application of a film coating is one of the most widely used methods during the preparation of solid dosage forms. The film-forming materials can be used as solutions (aqueous and organic), emulsions or suspensions (aqueous dispersions).[1] The effects of the film-forming properties of different systems of coating fluids (solutions or dispersions) and the effects of the structures of the films on the properties of the film formed are becoming well known.[2,3] The influence of the nature of the solvent and the roles of different additives on these properties also are widely evaluated. The applicability of aqueous solutions is restricted by the solubility of the polymers. Because of the special composition and sensitivity of the system, the processibility of aqueous dispersions is more complex than that of solution systems, but they nevertheless are the most popular forms.[4–7] Organic solutions of polymers were commonly used earlier, but these systems are nowadays less popular because of the associated environmental problems and the danger involved in the processing. In spite of these problems, a small amount of such volatile organic components (mainly ethanol) can be incorporated into liquids prepared from aqueous dispersions.[8] In certain cases, mixtures of water and a volatile solvent as cosolvent have been used to formulate solution systems.[9]

Numerous additives (plasticizers, colorants, pigments, antifoaming agents, etc.) are applied to change the properties of films and to increase the processibility of the liquids. It is particularly important to know the type, the solubility and the role of these for the permeable polymers. They are insoluble throughout the entire gastrointestinal tract, but swell in the fluids. In the swollen form, these polymers are permeable to water and dissolved ingredients.[10] Thus, factors that can change the structures of the films can appreciably alter the dissolution profile.

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The most frequently used aqueous dispersions of permeable polymers are those of acrylic polymers. Different types of acrylic polymers can be used for different purposes; their chemical structures determine the solubilities of these polymers.[9] Methacrylic ester copolymers are not soluble in the physiological pH range, but are permeable. Eudragit NE is a commonly used coating material, which contains this type of acrylic polymer. These materials can be applied for the preparation of matrix tablets, controlled-release buccal patches, controlled-release floating pellets, topical delivery systems and combination colonic drug delivery systems.[11–15] A number of physical and chemical stability problems are associated with the use of Eudragit NE.[16–18]

A problem that can arise during the preparation of a coating liquid is foam formation. An antifoaming agent can be applied to avoid the formation of small bubbles in the liquid, since foam formation in a coating liquid is likely to cause unevenness in the film, thereby modifying its protective function.[1] The effects of bubbles on films formed from aqueous dispersions have been evaluated previously.[19] These materials are mainly the water insoluble silicone derivatives (e.g., dimeticone, simeticone, etc.).[20] They have a low interfacial tension and thus it is thought that they are absorbed at the air/liquid interface in preference to the foaming agent, but they do not have the requisite ability to form a stable foam.[21] Thus, they can act as a barrier layer between the liquid and the air. In an optimum case, therefore, we consider that this may influence the evaporation of a volatile component from the liquid. Of course, this will hold only if the density of the antifoaming component is similar to (or lower than) that of the aqueous system.

The main objective of the present project was to evaluate the evaporation of coating liquids under definite circumstances. The barrier function of a polydimethylsiloxane antifoaming agent (Dimeticon E 1049) was studied its effect in via decreasing effect the weight loss of a stirred liquid containing a volatile component. Eudragit NE was used as an aqueous polymer dispersion, with ethanol as a volatile component, and different concentrations of antifoaming agent. The concentration of the antifoaming component was higher than generally used, but the possible importance of its effect can be studied more accurately at higher concentrations. The mass loss was measured during the stirring of the different liquids. The exact, mathematically determined effects of the different operational factors (stirring rate, duration, and quantity) were compared by means of a factorial design. The importance of these factors can be informative for determination of the optimum composition of the liquid and the optimum parameters for the constant stirring, because such stirring is generally necessary during film coating.

This type of information can be very important for the solution of different problems that arise with open systems. Open mixing tanks are often applied in formulation laboratories for the preparation of coating liquids and for constant stirring during atomization. Hermetically closed tanks can not be used during the coating process, since atomization is impossible from such systems. Knowledge of these data also can be utilized to decrease the danger involved in the processibility of liquids containing volatile organic components. The understanding of a process leads to the ability to identify the critical points of film coating control and to promote the development of appropriate devices.

TABLE 1
Compositions of liquids (percentages by mass)

	Liquid 1	Liquid 2	Liquid 3	Liquid 4
Eudragit NE 30 D	50%	50%	50%	50%
Ethanol 96%	—	20%	20%	20%
Water	50%	30%	27%	24%
Dimeticon E 1049	—	—	3%	6%

MATERIALS AND METHODS

Materials

Eudragit NE 30D (Degussa Pharma Polymers, Darmstadt, Germany) was applied as an acrylic polymer dispersion. Dimeticon E 1049 was used as an antifoaming agent. It is a polymethylsiloxane, which is practically insoluble in water and only very slightly soluble in ethanol.[20] The volatile component was ethanol (Spektrum-3D, Debrecen, Hungary). The compositions of the liquids are given in Table 1.

Mixing

The fluid was mixed with a stirring rod driven by an overhead stirrer (IKA-Werke GmbH & Co. Kg, Staufen, Germany). Glass beakers with identical dimensions (7.70 cm in diameter) were used as mixing tank.

A 2^3 full factorial design with a central point was applied to determine the effects of the operational parameters. The factors considered were the quantity of liquid, the stirring duration and the stirring rate. The values of these factors were identical for each of the liquids (Table 2).

Statistica for Windows 7.1 AGA (StatSoft, Inc. Tulsa, OK, USA) software was applied to determine the effects of the factors. The experiments were performed in a randomized

TABLE 2
Levels of factors

Factor	Low (−)	Zero (0)	High (+)
Quantityof liquid	100 g	150 g	200 g
Stirring duration	10 minutes	15 minutes	20 minutes
Stirring rate	300 rpm	450 rpm	700 rpm

TABLE 3
Evaporation of individual starting materials

Duration of evaporation (minutes)	Loss in mass of water (%)	Loss in mass of ethanol (%)	Loss in mass of Dimeticon E 1049 (%)	Loss in mass of Eudragit NE 30 D (%)
0	0	0	0	0
10	1.43 ± 0.14	7.09 ± 0.46	1.41 ± 0.05	1.37 ± 0.21
20	2.37 ± 0.36	11.65 ± 1.04	2.57 ± 0.06	2.15 ± 0.17
30	3.30 ± 0.41	18.56 ± 1.77	3.55 ± 0.10	2.85 ± 0.24
60	5.94 ± 0.95	34.12 ± 3.72	6.26 ± 0.10	5.33 ± 0.30
90	8.34 ± 1.25	48.18 ± 5.05	9.02 ± 0.12	7.48 ± 0.53
120	10.95 ± 1.68	63.27 ± 6.86	11.77 ± 0.23	9.94 ± 0.75

sequence. The following linear approach was applied to determine the surface of the response for the 2^3 factorial design.

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Study of Evaporation

The evaporation of the fluids was evaluated with an analytical balance in a climate room. The temperature was 21 ± 1°C and the relative humidity was 45 ± 1%. These conditions were constantly checked and controlled.

The mass losses of the individual starting components under these conditions were also studied. 5.00 g of liquid was poured into a Petri dish 7.0 cm in diameter. Their masses were measured after different periods of evaporation. Three parallel tests were performed.

RESULTS

The losses in mass of the individual components due to evaporation during 2 hours were first evaluated. The mass loss in every time was greatest for ethanol (Table 3). The quantity lost was very similar for the other three samples. The rate of evaporation for ethanol was about 6 times higher than those for the other samples.

The densities of Liquid 2 and Dimeticon were determined at 20°C. Their values were not appreciably different (0.986 ± 0.001 g/cm^3 for Liquid 2 and 0.990 ± 0.001 g/cm^3 for Dimeticon); hence because of the low interfacial tension, the covering of the liquid by Dimeticon was expected.

The different liquids exhibited very varied rates of evaporation (Table 4). In every case, the highest value was observed for a high stirring rate, a long stirring time and the lowest starting quantity. A very low rate of evaporation was detected for Liquid 1. The losses due to evaporation from Liquids 2, 3, and 4 were much higher (around 3–4 times tose Liquid 1). This was due to the more intensive evaporation of more volatile ethanol, up to nearly 15% of the incorporated ethanol being lost. Thus even a short stirring (20 minutes) dramatically changed the composition of the coating fluid. This can alter the behaviour of the coating film since it is well known that the presence of ethanol can change the structure of the film.[22] The effect of the antifoaming agent was not significant. In some cases, a small decrease was detected in the presence 6% of Dimeticon.

TABLE 4
Evaporation of different liquids

Stirring rate (rpm)	Duration (minutes)	Starting quantity (g)	Mass loss for Liquid 1 (%)	Mass loss for Liquid 2 (%)	Mass loss for Liquid 3 (%)	Mass loss for Liquid 4 (%)
300	10	100	0.205	0.630	0.752	0.606
700	10	100	0.301	2.203	2.352	1.830
300	20	100	0.313	1.385	1.193	1.199
700	20	100	0.804	3.523	3.553	3.044
300	10	200	0.067	0.294	0.269	0.287
700	10	200	0.126	0.623	0.568	0.549
300	20	200	0.108	0.470	0.460	0.507
700	20	200	0.219	1.047	1.151	1.162
500	15	150	0.216	1.073	0.756	0.921

TABLE 5
Effects of the factors

	Liquid 1	Liquid 2	Liquid 3	Liquid 4
R^2	0.9939	0.9958	0.9723	0.9927
Mean/Interc.	0.2620	1.2497	1.2282	1.1226
(1) Stirring rate	0.1894	1.1538	1.2374	0.9968
(2) Duration	0.1862	0.6689	0.6042	0.6595
(3) Starting quantity	−0.2756	−1.3270	−1.3504	−1.0433
1 by 2	0.1115	0.2028	0.2883	0.2536
1 by 3	−0.1041	−0.7013	−0.7425	−0.5382
2 by 3	−0.1192	−0.3685	−0.2169	−0.2432
1*2*3	−0.0860	−0.0792	−0.0918	−0.0570

The effects of the different factors were determined after the fitting of the response surface (Table 5), which enhanced the comparison. The fitting was very good for every sample. The mean of the results (intercept) was lowest for Liquid 1 and highest for Liquid 2. The antifoaming component slightly decreased the values. In each case, the most substantial factor was the starting quantity. The negative sign indicated that, on increase of the starting quantity, the amount evaporated decreased. This is very important because of the change in the quantity during the coating process.

For a better understanding of the phenomenon, the relative changes in the effects of the factors were studied (Table 6). The effect of ethanol can be assessed from a comparision of Liquid 1 and Liquid 2. It can be seen that variation of the stirring rate caused the most appreciable change, the increase due to this factor being about 6-fold. Thus, it is the most sensitive factor influencing the composition.

The changes in the other two factors were also significant, but the degrees of the increase were lower. The interaction of the factors exhibited a great variety. The effect of the three-factor interaction was lower for Liquid 2, but the importance of this could be neglected because of the low absolute value.

TABLE 6
Relative deviations of the effects of the factors (comparison of Liquid 1 with Liquid 2)

Factor	Relative deviation (%)
Mean/Interc.	476.96
(1) Stirring rate	609.13
(2) Duration	359.30
(3) Starting quantity	481.46
1 by 2	181.90
1 by 3	673.51
2 by 3	309.19
1*2*3	92.15

TABLE 7
Relative values of the effects of the factors (comparison of Liquid 2 with Liquids 3 and 4)

	Relative value for Liquid 3	Relative value for Liquid 4
Mean/Interc.	98.28	89.83
(1) Stirring rate	107.24	86.39
(2) Duration	90.32	98.59
(3) Starting quantity	101.76	78.62
1 by 2	142.19	125.06
1 by 3	105.88	76.75
2 by 3	58.87	65.99
1*2*3	115.84	71.88

The impact of the antifoaming agent was evaluated by a comparison of Liquid 2 with Liquids 3 and 4 (Table 7). It can be seen that the higher concentration of antifoaming component did not cause the importance of the factors to decline appreciably. A slight change was observed for the stirring rate and a slightly higher one for the starting quantity.

CONCLUSIONS

It can be concluded that the loss in mass of the volatile component from the free coating liquid during stirring was very low under the examined conditions. The evaporation increased considerably for the liquid containing 20% ethanol. In this case, about 15% of the volatile component was lost during the 20 minutes of stirring. Thus, the composition changed dramatically, and hence the properties of the film also differed. The highest rate of mass loss was detected when the stirring was fast, the duration was long and the starting quantity was small.

The presence of ethanol changed the relative importance of the operational parameters on the evaporation. The effects of the factors increased, but to different extents. The most sensitive factor was the rate of mixing, when a roughly 6-fold enhancement was detected. On application of the antifoaming agent, the evaporation significantly did not decreased. The alterations in the effects of the operational factors were not very appreciable. 6% of Dimeticon E 1049 caused only a 20% reduction in the effect of the starting quantity. The other changes in the effects of the factors were smaller: only the factor interaction veried more extensively.

Finally, it may be stated that the application of a polydimethylsiloxane antifoaming agent does not significantly change the evaporation in these systems containing ethanol as a volatile component. Thus, primarily the operational parameters must be considered during the formulation of these compositions.

This information helps in design of an appropriate device for stirring: our results indicate that the open systems are not adequate and it is known that a hermetically closed tank makes atomization impossible. Accordingly, a tank with a special air suppling valve is necessary, but in this case the evaporation of the volatile component can not be eliminated. In this system, the air space of the holder can be saturated with the volatile agent at the end of the process, because of the relative high volume of the pot. This can induce other problems, for example, explosion. Consequently determination of the critical control point and optimization of the coating are essential.

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III

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Pretreatment of pigments to prepare liquids for enteric coating

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Film coating fluids commonly contain different pigments. The objective of this work was a study of the distribution of these particles in the coating film. Different pretreatment forms (pigment suspension, pigment paste and untreated pigments) were applied. They were incorporated into a Eudragit® L 30 D-55 dispersion. The surface roughness and the mechanical properties of the free films indicated, that the most homogeneous film was obtained with the pigment paste. The homogeneity of the film was investigated by mechanical testing. The protective effect of the coating did not vary with the application of pigments in different forms, but the appearance of the coated tablets underwent a considerable change.

1. Introduction

Film-forming polymers in aqueous dispersions are increasingly utilized during the production of coated solid dosage forms (Cole et al. 1995). Various types of polymers can be used to form aqueous dispersions, and numerous water-soluble and insoluble additives are applied in the coating liquids (Bauer et al. 1988; Lehmann 1999; Nimkulrat et al. 2004). The mixing sequence for the preparation of a coating liquid containing insoluble particles is important. The insoluble materials can modify the properties of the film formed (Felton and McGinity 1999, 2002; Petereit and Weisbrod 1999; Plumb et al. 2002) and thus their homogeneous distribution is indispensable. The first step is the preparation of the pigment suspension (Eudragit Brochure 2005). Conventionally, the materials (glidants, pigments, plasticizers and other excipients) must be intensively homogenized in water with a high-speed mixing apparatus. Next, the homogeneous pigment suspension must be gently mixed with the polymer dispersion to prevent coagulation. Efforts are currently under way to make this process simpler and more effective. The application of ready-to-use preparations is currently spreading. One new possibility is a pigment paste which contains all the insoluble components with other additives as stabilizers of the paste.

2. Investigations, results and discussion

The aim of the present study was the evaluation of a conventionally prepared suspension and comparable suspensions prepared from a paste. These were incorporated into Eudragit® L 30 D-55 dispersions and were compared with a coating dispersion prepared without pretreatment of the pigments. Smoothness and mechanical properties of the free films were determined, the protective effect of the coating and the smoothness of the coated tablets.

It was observed that all of the parameters describing the surface roughness of the free films was best for the sample prepared with the paste (Table). The means of all parameters and also the deviations were the highest for the sample which did not undergo pretreatment. This can be explained by the insufficient distribution of the insoluble particles.

The surface roughness of the uncoated tablets (Ra: 2.46 ± 0.46 μm; Rq: 3.11 ± 0.63 μm; Rz: 14.49 ± 3.23 μm) was lowered by application of a coating fluid containing a pigment paste. The values were significantly ($p < 0.05$) lower for sample S2. Sample S3 once again exhibited the highest values and deviations for every parameter.

The mechanical properties of the poured films were different. Not only the deformation force, but also the characteristics of the curve changed (Fig). A sharp break was detected for S2 and a less sharp one for S3. A sharp deformation point indicates a very rapid modification of the film structure. Inhomogeneity in the structure leads to the formation of small film areas without solid particles or with more solid particles with different mechanical properties. The break points for such samples are therefore less sharp. The difference between S1 and S3 may well be due to the more homogeneous distribution of the different components in S1.

The lowest deformation force was detected for S2, possibly because of the paste-stabilizing component (e.g. preservative). The relative deviation of this parameter was also the highest for S3. This may be explained by the lower degree of homogeneity.

Table: Surface roughness of the product (n = 10)

Sample	Ra (μm)	Rq (μm)	Rz (μm)
S1 (film)	4.21 ± 0.98	5.47 ± 1.46	28.24 ± 6.52
S1 (tablet)	2.60 ± 0.38	3.32 ± 0.54	12.89 ± 2.72
S2 (film)	3.60 ± 0.24	4.44 ± 0.29	22.40 ± 3.02
S2 (tablet)	1.43 ± 0.34	1.73 ± 0.36	6.39 ± 1.44
S3 (film)	5.36 ± 5.68	7.70 ± 8.37	37.06 ± 30.64
S3 (tablet)	3.71 ± 1.17	4.54 ± 1.26	14.88 ± 3.61

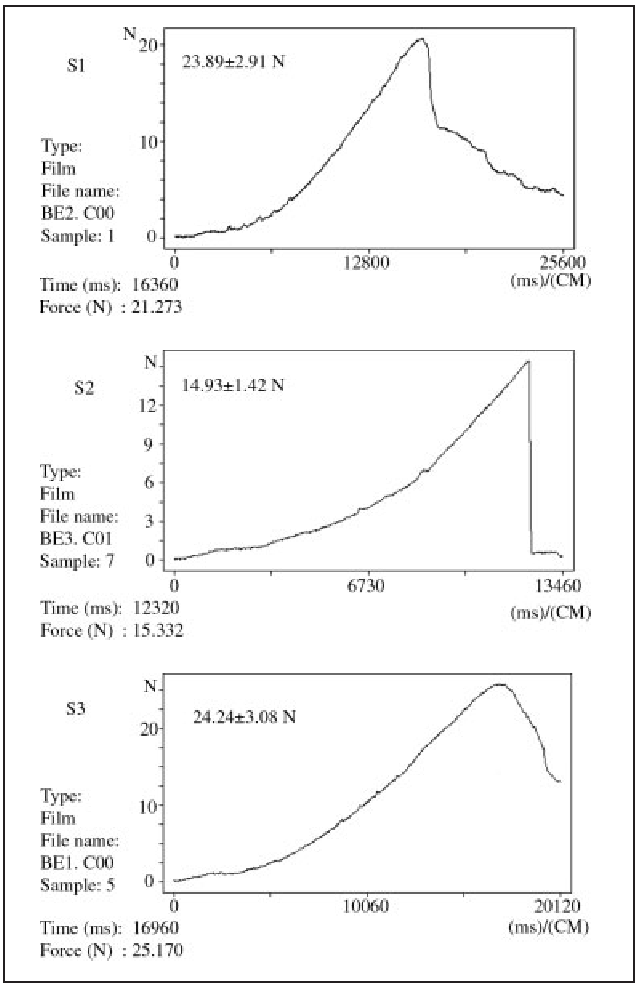

Fig.: Deformation curves of free films

The protective effect of the film (dry polymer content: 4 mg/cm^2) on the surface of the tablets was appropriate for all of the samples, independently of the surface roughness, since disintegration of the tablets in gastric juice was not detected.

It may be concluded that pretreatment of the pigments is important because surface roughness can differ significantly on change of the preparation method. Neglect of this step can result in a changed appearance of the product. A more homogeneous film can be achieved by the application of a pigment paste. The characteristics of the deformation curve are informative in the evaluation of the homogeneity of the film. The application of new ready-to-use pastes is a suitable method because the preparation is rapid and the film formed is smooth and homogeneous. However, the paste-stabilizing components change the properties of the film. Optimization of the preparation of pigments without additives is therefore also necessary.

3. Experimental

3.1. Materials

The aqueous polymer dispersion was the methacrylic acid copolymer Eudragit® L 30 D-55 (Degussa Pharma Polymers, Darmstadt, Germany). A pigment paste (W.A.S.-L – White, Rofarma Italia S.r.l., Milano, Italy) containing talc, titanium dioxide, triethyl citrate, propane-1,2-diol, alginate and potassium sorbate, with a solid content of 77.45%, was applied. The conventionally prepared pigment suspension contained titanium dioxide, talc, triethyl citrate (suggested ratio for Eudragit® L (Eudragit Brochure 2005)) 0.3% dimeticone (type E1049 a gift from EGIS Pharmaceuticals PLC) as antifoaming agent and 0.05% iron oxide (Sicovit Red, BASF GmbH, Ludwigshafen, Germany) as colouring pigment.

3.2. Preparation of products

The solid content of each of the coating dispersions was 20% (10% pigment + 10% polymer). Each sample contained colouring pigment for evaluation of the effect of iron oxide.

S1: The pigment suspension was prepared by mixing with an Ultra-Turrax (IKA-Werke GmbH & Co. KG, Staufen, Germany) at 20,000 rpm for 10 min. After this, the pigment suspension was poured into the polymer dispersion and mixed with an overhead stirrer (IKA-Werke GmbH & Co. KG).

S2: Sicovit Red was dispersed in water with Ultra-Turrax mixing (20,000 rpm) for only 1 min. The Ultra-Turrax was not used further. The W.A.S.-L paste was then added to the dye suspension, which was next poured into the polymer dispersion and mixed with an overhead stirrer.

S3: For comparison, a “base sample” was also prepared, where the S1 components were mixed with an overhead stirrer. The Ultra Turrax was not used.

The coated tablets were prepared in a pan coater (Bohle BFC, LBBohle, Ennigerloh, Germany). The process parameters were kept constant for all batches.

3.3. Evaluation of products

The surface roughness of the tablets and films was determined with a Mitutoyo SJ-201P tester (Mitutoyo Co., Kawasaki, Japan). An evaluation length of 0.8 mm was applied for tablets, and of 2.5 mm for films. For this test, free films were prepared. The liquid was atomized onto a glass surface (Ra: 0.10 ± 0.03 μm; Rq: 0.13 ± 0.03 μm; Rz: 1.23 ± 0.38 μm). The arithmetic mean deviation (Ra), root-mean-square deviation (Rq), and maximum height of the profile (Rz) were determined. 10 parallel tests were performed.

The breaking hardness of poured films prepared on a teflon surface was tested. The strength tester and the software were developed in our institute (Bajdik and Pintye-Hódi 2006; Bajdik et al. 2007). Ten tests were performed in parallel.

The enteric resistance was evaluated via the time of tablet disintegration, measured with an Erweka ZT 71 (Erweka GmbH, Heusenstamm, Germany) apparatus, in HCl solution at pH 1.2.

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IV

EVALUATION OF FACTORS AFFECTING THE MIXING OF A POLYMER DISPERSION AND A PIGMENT SUSPENSION TO PRODUCE A COATING LIQUID

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ABSTRACT

The widely-used coating liquids contain a pigment suspension and a polymer dispersion. The first step in the suggested mixing sequence for the preparation of these liquids is the preparation of the pigment suspension, which must then be gently mixed with the polymer dispersion. The main objective of this study was to establish parameters that can be applied for this mixing. Different operational parameters were evaluated by factorial design. The homogeneity of the liquid prepared and dimensions of the vortex cone formed was evaluated. It was concluded that the homogeneity of the coating liquid was very sensitive to the operational parameters, the most important of which was the stirring speed. The other factors evaluated did not influence the process directly, but only via their interactions. It may be stated, that the 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 the influencing factors and modification of the vortex cone must be separately performed for determination of the optimum operational parameters of processing of the coating liquid.

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Keywords: aqueous polymer dispersion, homogeneity, mixing, pigment suspension, vortex cone

INTRODUCTION

A thin polymer-based film coating is often applied to a solid dosage form (tablets, capsules or granules). Film-forming macromolecules can be formulated into solutions (water or organic solvent base) or aqueous dispersions /1/. The effects of the film-forming properties of different systems of coating fluids (solutions or dispersions) and the effects of the structures of the films on the properties of the film formed are becoming well known /2-4/. Various types of polymers (cellulose derivatives, poly(methacrylates), poly(vinyl) derivatives, etc.) can be used to form aqueous dispersions, but the best-evaluated are acrylic acid derivative polymers /5/. Numerous water-soluble and insoluble additives (plasticizers, colorants, pigments, antifoaming agents, etc.) are utilized to change the properties of films and to increase the processibility of these liquids. The water-insoluble additives are applied in these aqueous dispersions for the preparation of polymer films for different purposes. It is recommended to add an insoluble glidant (e.g. talc, magnesium stearate, etc.) to the suspension to avoid sticking /6/. Insoluble pigments (e.g. iron oxide, titanium dioxide, etc.) are also applied to ensure the appropriate appearance of the coated product /7/. They can modify the properties of the film formed /8-10/ and thus their homogeneous distribution is indispensable.

The suggested mixing sequence for the preparation of a coating liquid containing insoluble particles is very important. According to a manufacturer of dispersions, the first step is the preparation of the pigment suspension /11/. In this case, the intensive homogenization of the materials (glidants, pigments, plasticizers and other excipients) in water must be performed with a high-speed mixing apparatus. After this, the freshly prepared homogeneous pigment suspension must be gently mixed with the acrylic dispersion. High-speed mixing can cause precipitation of the polymers, and this apparatus can therefore not be used in this step /12/. The even distribution of the insoluble particles in the pigment suspension is very important because gentle mixing cannot disrupt pigment aggregates. The main cause of the problems during the preparation of these liquids is the fact that the definition of "gentle mixing" is not clear-cut.

The main objective of our project 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. The effects of the conditions (the mixing volume, the dimensions of the mixing tank, the type of mixing apparatus, the stirring time, the stirring speed, etc.) must be evaluated. The effects of high-speed stirring on the properties of aqueous dispersions were evaluated earlier /13, 14/. We have now examined the preparation of a complex coating suspension. An exact knowledge of the effects of the technological parameters used during the formulation of a liquid containing a pigment suspension is very important with a view to increasing the processibility of insoluble particles in a coating liquid.

The other objective is the mathematical study of the mixing of these types of liquids. It is well known that a vortex cone is formed during mixing. Studies of this phenomenon have been reported in publications dealing with physics and chemical engineering /15-17/, but it has been rather neglected in the pharmaceutical technology. This question and the effectiveness of mixing are dealt with in the present study.

Titanium dioxide, applied as an insoluble additive in our study, is widely used in pharmaceutical formulations as a white pigment. Because of its high refractive index, titanium dioxide has light-scattering properties that may be exploited in its use as a white pigment and opacifier. The range of light that is scattered can be altered by varying the particle size of the powder. For an appropriate protective effect, the even distribution of the particles is necessary /18/. A high-speed Ultra-Turrax mixer was used to disperse the powder in water. The optimum mixing parameters were determined previously /19/. Eudragit NE 30D was applied as a widely-used and evaluated acrylic polymer dispersion, which forms a permeable film /20-22/. The pigment suspension, polymer dispersion and water were mixed with a magnetic stirrer. The dimensions of the mixing tank were constant but the operational parameters (stirring speed, time, quantity and stirrer size) were different. The homogeneity of the liquid was evaluated with a gravimetric method. The dimensions of the vortex cone formed were also studied. The exact, mathematically-determined effects of different factors were evaluated by means of a factorial design. The effects of the changes in homogeneity and size of the vortex cone were compared.

MATERIALS AND METHODS

Materials

Titanium dioxide (Merck GmbH, Darmstadt, Germany) was applied as an insoluble material. These particles were smaller than 10 μm (D10=0.1 μm; D50=0.5 μm, D90=1.3 μm). It was dispersed in distilled water at a concentration of 10%. Eudragit NE 30D (Degussa Pharma Polymers, Darmstadt, Germany) was applied as a polymer dispersion. Eudragit NE 30 D contains 28.5-31.5% dry matter (poly (ethyl acrylate, methyl methacrylate) 2:1) and approximately 1.5% Nonoxynol 100 as emulsifier. The composition of the liquids was as follows:

20% pigment suspension
30% polymer dispersion
50% water

The pigment suspension was prepared with an UltraTurrax mixer according to our previous results (quantity: 100 g; stirring speed: 17,500 rpm; time: 10 min) /19/.

Mixing

The fluid was mixed in identical cylindrical glass beakers (7.70 cm in diameter) with a magnetic stirrer (IKA-Werke GmbH & Co. Kg, Staufen, Germany). The mixing sequence was as recommended by the manufacturer (the pigment suspension was added to the polymer dispersion).

A 2^4 full factorial design was first 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 (in grams).

Secondly a 2^3 full factorial design with a central point was used to determine the factors affecting the volume of the mixing whirlpool. The factors were the quantity, the stirring speed and the stirrer size. The values of the factors were similar to those in the previous evaluation.

Statistica for Windows 7.1 AGA (StatSoft, Inc. Tulsa, USA) software was applied to determine the effects of the factors. The experiments were performed in randomized sequence. The following linear approach was applied to determine the surface of the response for the 2^3 factorial design:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

while that used to determine the surface of the response for the 2^4 factorial design was:

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{123}X_1X_2X_3 + b_{234}X_2X_3X_4 + b_{124}X_1X_2X_4 + b_{134}X_1X_3X_4$$

Determination of homogeneity

The solid content at the bottom of the sample holder was determined by a gravimetric method: 5 ml of liquid was taken out with an automatic pipette. The sampling sites were similar (at the bottom of the beaker, next to the wall). The samples were dried at 105 °C in a heating chamber. The liquids and the dried samples were weighed with an analytical balance. Three parallel measurements were performed.

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 absolute value of relative deviation can be calculated according to the following equation.

$$(\text{average measured concentration} - 17.033) \times 100/17.033$$

Study of the vortex cone

Callipers with an accuracy of 0.02 mm were used to determine the volume of the whirlpool induced by mixing. The height of the liquid was measured during homogenization and without the mixing. The volumes were calculated from the results. The difference in these parameters can be attributed to the volume of the vortex cone generated by the turbulent movement of the stirrer.

The thickness of the foam was also measured with these callipers with an accuracy of 0.02 mm. Three parallel measurements were performed.

RESULTS

Table 1

Levels of factors

Factor	**Low (-)**	**Zero (0)**	**High (+)**
Quantity	100 g	150 g	200 g
Time	10 min	15 min	20 min
Stirring speed	400 rpm	700 rpm	1000 rpm
Stirrer	1.73 g (ca. 0.6 cm^3)	2.65 g (ca. 0.9 cm^3)	3.43 g (ca. 1.2 cm^3)

It can be seen from the results of the homogeneity tests that the deviation of the solid content from the calculated value exhibited great variation (0.01-24.25%) (Table 2). The determination of the response surface (R^2=0,9991) demonstrated the relative importance of the various factors (Figure 1). 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.

Table 2

Relative deviation of solid content of sample

X1 Quantity (g)	**X2 Time (min)**	**X3 Stirring speed (rpm)**	**X4 Stirrer (g)**	**Relative deviation (%)**
100	10	400	1.73	17.30
200	10	1000	1.73	1.25
100	20	1000	1.73	0.17
200	10	400	3.43	15.75
200	20	400	1.73	11.25
100	10	400	3.43	1.75
100	20	400	3.43	17.00
200	10	1000	3.43	0.01
200	20	400	3.43	20.75

100	20	400	1.73	14.75
100	10	1000	1.73	4.33
100	20	1000	3.43	3.50
200	10	400	1.73	24.25
200	20	1000	1.73	2.50
200	20	1000	3.43	1.00
100	10	1000	3.43	9.33

During mixing, the liquid must be in constant motion for the homogeneous distribution of the insoluble particles. Previous results revealed that the factors affecting intensiveness of moving were more important 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. These factors can be changed in different ways e.g. it is well known that the viscosity depends on the shearing and also the temperature /23/. Overall, it can be concluded 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.

Because of the large number of parameters, an exact mathematical description of the motion of the liquid is very difficult, and the choice of the optimum technological parameters for the production of a homogeneous fluid is not easy. Very sophisticated or indirect (less exact) methods can be used for their determination. An important feature of the motion of the liquid is the vortex formed during mixing. The volume of this vortex can be easily determined during homogenization. Accordingly it was chosen for evaluation as an investigated parameter in this study. The previously used factors (except time) were also applied. The explanation of the exception was that this factor was the least important individual one. The liquid and the values of the factors were the same as in the homogeneity testing.

It can be seen from the results that the vortex volume varied considerably (0.448 – 6.527) with the different set-ups (Table 3). The effects of the factors also very differed greatly. The highest value was detected for the mixing speed (Figure 2). The fitting was very good (R^2=0,9632), but the factors and their interactions were not significant.

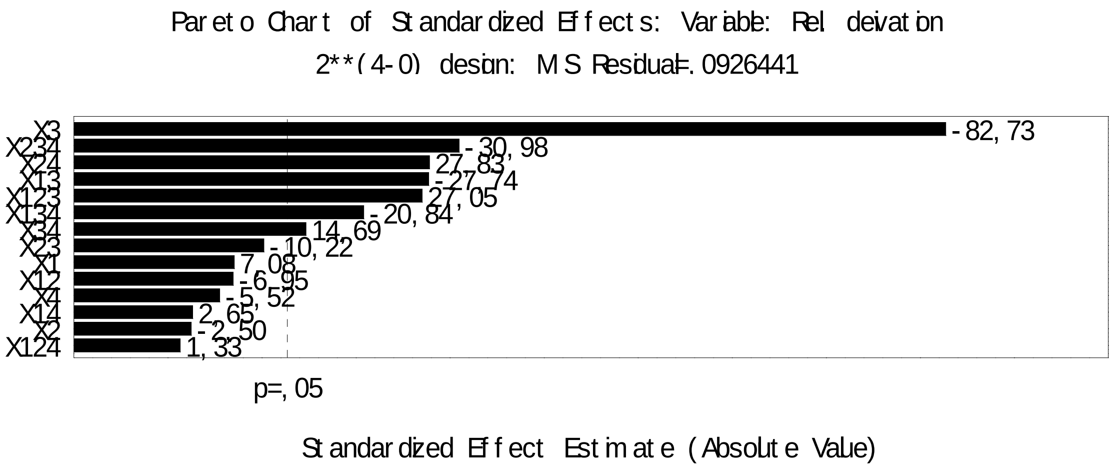

Fig. 1: Effects of the various factors on relative deviation

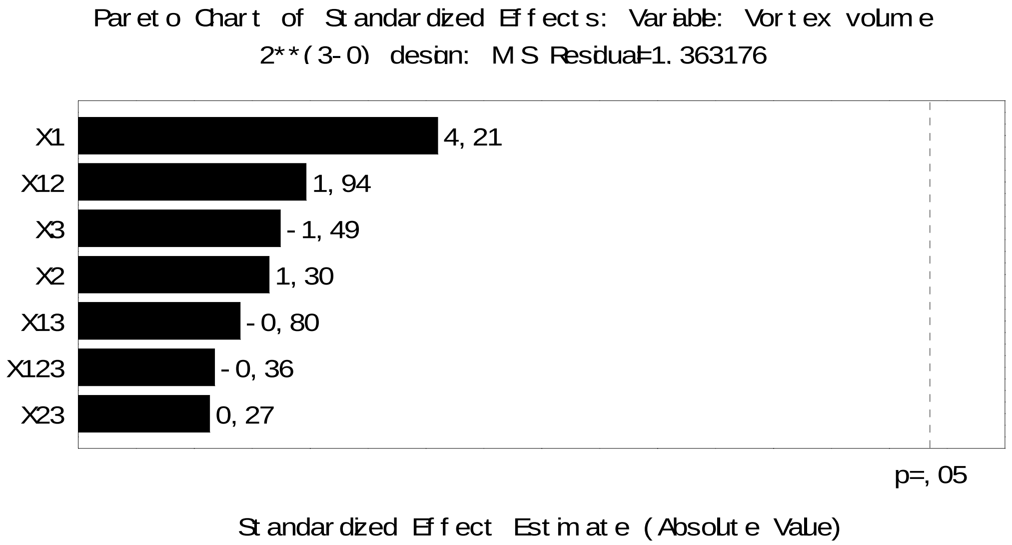

Fig. 2: Effects of the various factors on volume of vortex cone

Table 3

Volume of the vortex cone

Stirring speed (rpm)	**Stirrer (g)**	**Quantity (g)**	**Vortex volume (cm^3)**
400	1.73	100	1.549
1000	1.73	100	3.787
400	3.43	100	0.502
1000	3.43	100	6.527
400	1.73	200	0.457
1000	1.73	200	1.967
400	3.43	200	0.448
1000	3.43	200	4.566
700	2.65	150	1.237

The effects of the factors in the homogeneity tests and the vortex cone were compared. It can be concluded that there was no obvious connection between the results of the two experiments (Figure 3).

The explanation of the difference can be observed during the stirring of the water (Figure 4). It can be seen that not only the size of the cone differed, but also its shape. The height of the cone was similar, but it was narrower for the smaller stirrer. The difference was more relevant than the change in the volume.

The altered shape led to differences in the surface of the liquid, which can induce additional problems, e.g. the greatest higher possibility of foaming and evaporation of the liquid, etc. The importance of evaporation of components was tested in our previous study /24/. The thickness of the foam at the wall of the mixing tank was determined for 200 g of coating liquid. A higher speed (1000 rpm), the larger stirrer induced a thicker foam (Figure 5). This can be explained by the wider vortex cone, which exhibited a larger surface.

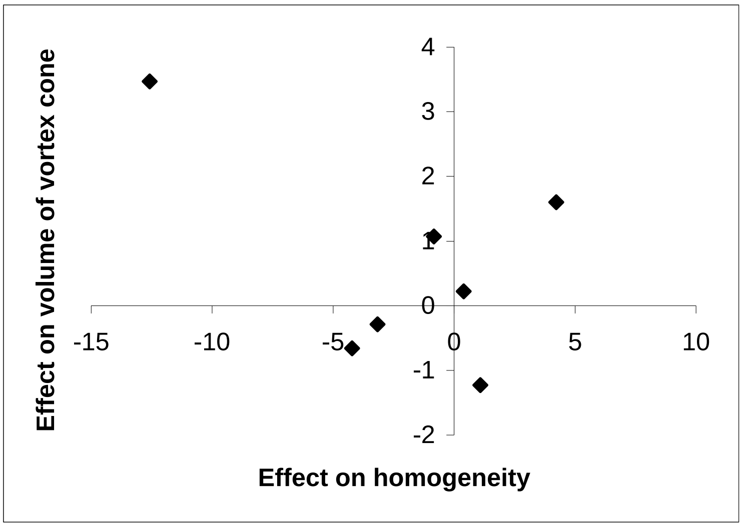

Fig. 3: Comparison of effects of factors

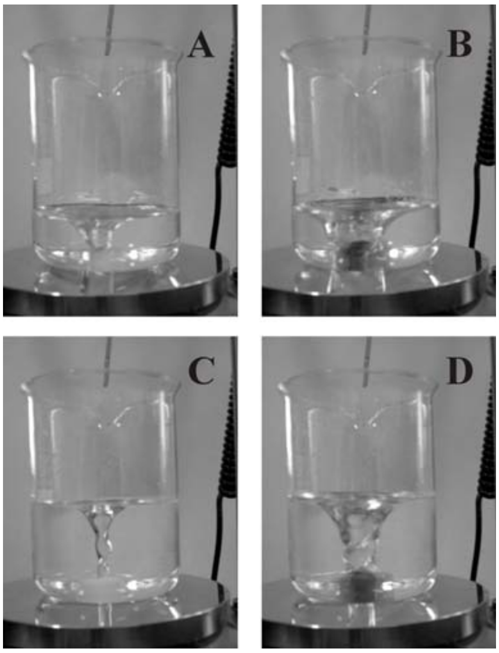

Fig. 4: Comparison of the vortex cone during the stirring of water (A - quantity: 100 g; stirrer: 1.73 g; B - quantity: 100 g; stirrer: 3.43 g; C- quantity: 200 g; stirrer: 1.73 g; D - quantity: 200 g; stirrer: 3.43 g)

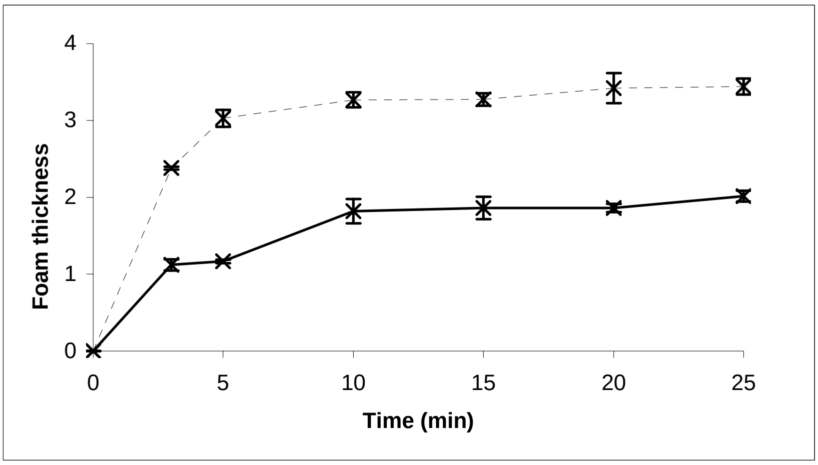

Fig. 5: Change in foam thickness as a function of time (continous line - 1.73 g stirrer, dotted line - 3.43 g stirrer)

CONCLUSIONS

It can be concluded that the homogeneity of the coating liquid is very sensitive to the operational parameters. The most important was the stirring speed. The effects of the other evaluated factors were not direct ones: they influenced the process via their interactions. The constant motion of the liquid was very important for the liquid containing insoluble particles. Because of the complex connections and interactions of the factors, a description of the optimum movement of the liquid is very difficult. For an evaluation of the turbulence, the vortex cone formed was studied. The changes in the dimensions of the cone during mixing are informative, but the homogeneity must be tested previously because there is no obvious relationship between these parameters. The homogeneity problems mainly can be eliminated by factors affecting the intensiveness of motion. They cannot be changed by the mixing time. Application of the applied test method revealed other problems which can arise during mixing, e.g. foaming. The homogeneity of the liquid cannot be predicted directly from the physical features of whirlpool formation.

The importance of the quantity of the liquid must be considered, because the volume of the liquid decreases during coating and thus the other parameters must also be altered to maintain mixing with constant efficiency without unwanted effects (e.g. foaming). An exact mathematical evaluation of the influencing factors and their interconnections is very important for determination of the optimum operational parameters for the processing of this liquid and the critical control points of film coating.

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Felületen lejátszódó jelenségek szerepének vizsgálata a bevonó folyadékok előállítása során

BÖLCSKEI ÉVA, BAJDIK JÁNOS, *HÓDI KLÁRA

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Summary

Bölcskei. É., Bajdik, J., Hódi, K.: ***Evaluation of phenomena detected on the surface of stirred coating liquid***

The main objective of this work was to study the effect of conditions of coating fluids through the properties of the coating fluid, film and coated product. With a more accurate understanding of the process the effects of the factors can be defined and by means of this the optimal composition can be determined and problem-free coating can be carried out. In this work the evaporation was studied. The effects of different operational factors on evaporation were studied through fluids of different compositions. In case of fluids containing ethanol a significant loss can be detected after a short period of time and this fact cannot be changed by the use of an antifoaming agent. The highest difference in effect of a given factor was detected for the stirring rate. The effect of the operational factors changed depending on the composition. Stirring rate showed the highest sensitivity to the presence of the volatile component. These results can help to determine the critical control points and the optimal stirring circumstances.

Összefoglalás

Munkánk során a bevonó folyadék, film és bevont termékek tulajdonságain keresztül tanulmányozzuk a bevonó szuszpenzió előállítási körülményeinek hatását. Célunk, hogy a folyamat pontosabb megértésével definiáljuk azokat a faktorokat, amelyek segítségével az optimális összetétel definiálható és a problémamentes bevonás megvalósítható. A munka ezen részében a keverés során fellépő felületi jelenségek közül a párolgást vizsgáltuk. Az egyes keverési paraméterek párolgásra kifejtett hatását különböző összetételű folyadékok esetén tanulmányoztuk. A 96%-os etanol tartalmú folyadékok esetén már rövid idő alatt is jelentős veszteség figyelhető meg és ezt a felületen feldúsuló habzásgátló is csak csekély mértékben képes megváltoztatni. A műveleti paraméterek közül a legjelentősebb a keverési sebesség volt. Az egyes keverési faktorok hatása az összetétel függvényében változott. Az illékony komponens jelenlétére a keverési sebesség mutatta a legnagyobb érzékenységet. Az itt nyert megállapítások – összekapcsolva a homogenitás vizsgálatok eredményeivel – hozzásegítenek a kritikus pontok megismeréséhez és így az optimális keverési körülmények definiálásához.

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VI

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Testing of the structure of macromolecular polymer films containing solid active pharmaceutical ingredient (API) particles

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ABSTRACT

The aim of the present study was to investigate the structure of free films of Eudragit® L 30D-55 containing different concentrations (0%, 1% or 5%) of diclofenac sodium by positron annihilation spectroscopy. The data revealed that the size of the free-volume holes and the lifetimes of *ortho*-positronium atoms decreased with increase of the API concentration. Films containing 5% of the API exhibited a different behavior during storage (17 °C, 65% relative humidity (RH)) in consequence of the uptake of water from the air.

1. Introduction

Polymer films play a very important role in the production of certain pharmaceuticals, e.g. coated and modified-release dosage forms. The objective of these orally administered forms is to control the release of the therapeutic agent and hence the drug absorption from the gastrointestinal tract. Such a dosage form effectively reduces adverse effects associated with peak plasma concentrations beyond that needed for therapeutic effectiveness, while maintaining the plasma level above or at that needed to achieve the therapeutic effect for a longer period.

Another important field is mucoadhesive films, where the API incorporated in the film layer is absorbed from the buccal mucosa in order to achieve a local (e.g. antibacterial) or a rapid systemic effect, avoiding the first-pass effect. Mucoadhesive polymers have been extensively studied as a means of prolonging the residence time of the dosage form on the adsorbing membrane and of localizing the drug in a particular region (Tamburic and Graig, 1995), thereby improving and enhancing its bioavailability; the concept of buccal mucoadhesion has therefore received considerable interest in formulation science (Mathiowitz and Chickering, 1999). Several approaches have been explored to obtain buccal mucoadhesive dosage forms as a platform for the controlled delivery of drugs (Nagai and Machida, 1985). During the preparation of a coating layer, it is necessary to know its physicochemical properties, e.g. its glass transition temperature, minimum film-forming temperature, flexibility and surface properties, how the API particles are located in the structure of the film-forming polymer and whether these particles modify the properties of the film formed. The presence of insoluble particles in the coating liquid can modify the resulting film (Petereit and Weisbrod, 1999; Felton and McGinity, 2002). The APIs in the film layer are mostly in solid form and rarely in dissolved form; the particle size of the API is therefore crucial, and the use of microcrystalline forms is recommended. In the present study, the aim was to prepare free films containing an API and to investigate the structure of the films by positron annihilation lifetime spectroscopy (PALS).

PALS is a unique method in the field of polymer studies. It is a microscopic method for study of the structure of polymers; however, it does not really examine the polymer itself, but the free volume between the polymeric chains. If the free-volume structure is disturbed by swelling, physical aging or the addition of active substances, the lifetime spectra react very sensitively to the changes (Süvegh et al., 1999; Deng and Jean, 1993; Pintye-Hódi et al., 2006). Thus, PALS provides complementary information on the polymer structure additional to that resulting from classical characterization methods.

1.1. *Positron annihilation lifetime spectroscopy (PALS)*

Positrons are the antiparticles of electrons. When a positron meets an electron, they undergo mutual annihilation and provide information on the surroundings of the annihilating pair. In materials, the probability of such a meeting depends on the electron density around the positron. In polymers, the electron density at any site is determined by the vicinity of polymeric chains; hence, positrons are exceptionally sensitive to free volumes.

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In polymers, a large proportion of injected positrons form a bound state with electrons before their annihilation (Süvegh et al., 1999). One of the bound states, the *ortho*-positronium atom or *o*-Ps, has a "long" lifetime: in polymers it lives for 1–3 ns. This lifetime is long enough for *o*-Ps atoms to scan their surroundings and, fortunately, it is long enough to be conveniently observed. Moreover, according to a simple model, the lifetime of an *o*-Ps atom depends on the size of the free volume in which it is located (Deng and Jean, 1993; Eq. (1))

$$\tau=\frac{1}{2}\left[1-\frac{R}{R+\Delta R}+\frac{1}{2\tau}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \quad (1)$$

Here, τ is the lifetime of the *o*-Ps, R is the radius of the (expectedly) spherical free-volume holes and ΔR is a constant. The equation indicates that the lifetime of *o*-Ps atoms increases with the size of the free-volume holes. Note that the number 1/2 has a dimension (namely nanoseconds) in this equation.

The above equation provides the most important tool via which to gain information on a polymeric sample by positron lifetime spectroscopy. The *o*-Ps lifetime is correlated directly with the size of the free-volume holes in the material. Thus, any change in the free volume is reflected in the *o*-Ps lifetime. Although the chemical composition of a polymer may affect the lifetime a little (Süvegh et al., 2000), *o*-Ps atoms provide the most direct information on the size of free-volume holes for polymers.

There are two ways to gain information on free volumes from PALS spectra. The easier is to assume that every *o*-Ps atom is located in uniform holes before annihilation. Although this assumption is definitely wrong for amorphous polymers, it does provide a stable average lifetime (and free-volume size). Moreover, this average lifetime reacts subtly to the changes in the free volume.

The other possibility is to try to find the exact lifetime distribution. Although this requires much more calculation and sometimes furnished unstable intensities, the results obtained are usually worth the effort. With this method, we can acquire more detailed information on the distribution of the size of free-volume holes, i.e. on the arrangement of polymeric chains.

2. Experimental

2.1. Materials

Eudragit® L 30D-55 (Evonik Röhm GmbH, Pharma Polymers, Darmstadt, Germany), is an aqueous dispersion of anionic polymers with methacrylic acid functional groups. The coating liquid compositions contained titanium dioxide, talc, triethyl citrate (the suggested ratio for Eudragit® L (Eudragit brochure)), dimethicon (type E1049, a gift from EGIS Pharmaceuticals Plc.) as antifoaming agent, and microcrystalline diclofenac sodium (Amoli Organics Pvt. Ltd.) in different proportions as API. Table 1 presents the compositions of the samples.

Table 1
Compositions of the samples.

		Sample 1 (g)	Sample 2 (g)	Sample 3 (g)
I	**Diclofenac sodium**	0.00	1.00	5.00
	Talc	6.56	6.49	6.23
	Titanium dioxide	1.79	1.77	1.70
	Triethyl citrate	1.31	1.30	1.24
	Dimethicon	0.34	0.33	0.32
	Purified water	28.34	28.05	26.92
II	**Eudragit® L 30D-55**	33.34	33.00	31.67
	Purified water	28.34	28.05	26.92

2.2. Preparation of samples

The solid content of each coating dispersion was 20%. The first step was the preparation of the pigment suspension (Eudragit brochure). Conventionally, intensive homogenization of the materials (glidants, pigment, plasticers and other excipients, including the API) in water must be performed with a high-speed apparatus. After this, the homogeneous pigment suspension must be gently mixed with the polymer dispersion to prevent coagulation. The pigment suspension containing 0%, 1% or 5% of the API was prepared through Ultra-Turrax (IKA-Werke GmbH & Co. KG, Staufen, Germany) mixing (17,500 rpm) for 10 min. After this, the suspension was poured into the polymer dispersion and mixed with an overhead stirrer (IKA.-Werke GmbH & Co. KG) at 210 rpm for 15 min (Bajdik et al., 2008). As a final step, the mixture was sieved.

The free films were prepared by pouring the mixture onto a Teflon surface, and drying it at room temperature (24 ± 1 °C, relative humidity 37% RH) for 48 h. The films were tested by PALS after various storage periods (1, 2 or 3 weeks at 17 °C and 65% RH).

2.3. Positron lifetime measurements

The positron source applied for the measurements was made of carrier-free ^{22}NaCl. In this case, the radioactive nuclide ^{22}Na emits positrons that penetrate the sample material. The active ^{22}NaCl was sealed between two very thin (5 μm) titanium foils, which ensured that 90–95% of the emitted positrons penetrated the studied polymer samples. The activity of the source was around 4×10^5 Bq.

Positron lifetime spectra were recorded with a fast–fast coincidence system (Mackenzie 1990). The system was constructed from standard ORTEC electronic units, and detectors were made from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps. Spectra were collected in 4096 channels of a computer-based multichannel analyzer card. The channel time was around 10 ps.

The collected lifetime spectra were evaluated and three lifetime components were extracted from them by the computer code RESOLUTION (Kirkegaard et al., 1981). The shortest two of these lifetimes are very hard to interpret in polymers. They represent the annihilation of free and trapped positrons and the short-living positronium state. In our study, we used the third component, the longest-living positron state. This lifetime reflects the annihilation of *o*-Ps atoms and is the most reliable parameter of lifetime spectra in the case of polymers. The intensity of this lifetime component was around 10% and did not change significantly during our study.

For the determination of lifetime distributions, we applied a variant of the code MELT (Shukla et al., 1993). This applies the maximum entropy method to determine lifetime distributions. The results were stable, but instead of the three previously assumed lifetimes, they revealed a fourth component, indicating a new positronium state. This fourth peak proved to be quite important for the understanding of the structure of the studied films. Although the exact origin of this peak is unclear, it proved to be connected with sites of Eudragit films where diclofenac-Na molecules are situated during film formation.

3. Results and discussion

The *o*-Ps lifetime data (Fig. 1) suggested that the films containing the API are formed in a metastable structure.

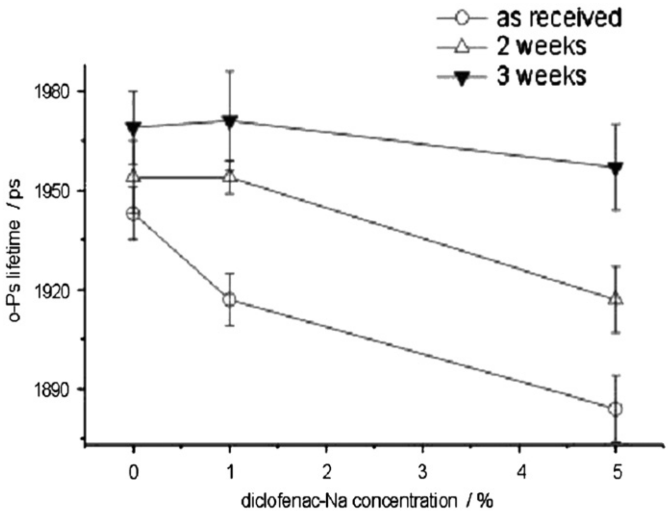

Fig. 1. *o*-Ps lifetimes in films containing different amounts of the API. The API distorts the original polymer structure, but as time goes by, the metastable structure relaxes and it is almost totally restored after 3 weeks of storage.

As more and more API was added to the film, the original free-volume structure of the polymer was gradually destroyed and the free-volume holes became smaller. However, the distortion was not permanent. While the Sample 1 film did 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 became independent of the amount of the API.

These conclusions drawn from the average lifetimes were largely supported by the results obtained on the lifetime distributions (Figs. 2 and 3), but the picture was made clearer. Even the Sample 1 film displayed significant aging effects during the storage period. The extra peak first moved towards longer lifetimes and widened a little. It then moved backwards and sharpened again. The large peak around 2 ns exhibited opposite behavior (Fig. 2). It should be noted that the lifetimes in Fig. 1 are the averages for the peaks in Fig. 2.

The shifting of peaks may indicate the effects of water uptake by the film (Zelkó et al., 2006). Such water molecules initially destroyed the original polymeric structure, but a new structure was later formed, involving hydrogen-bonds between water molecules and the polymeric chains.

The structural changes were more dramatic for the films containing a large amount of the API (Fig. 3).

The API distorted the structure of the Eudragit® L 30D-55 film significantly. The peaks were much wider indicating a more scattered distribution of the free-volume holes. Moreover, the extra peak was shifted considerably towards longer lifetimes and its intensity decreased. During storage, the two positronium states reacted differently to aging. The peak at 2 ns, indicative of *o*-Ps atoms situated in holes between polymeric chains, shifted a little towards longer lifetimes, demonstrating relaxation of the structure and on increase in size of the free-volume holes. This was most probably due to the plasticizing effect of water molecules absorbed from air.

On the other hand, the extra peak reacted strangely. It first split into two; the original peak then disappeared, and the new peak became higher. This alteration in the peaks indicates a process in which the original structure was transformed slowly to a new arrangement of molecules. As nothing similar happened in the pure film, the observed structural transformation was definitely connected with the API. We assume that the absorbed water molecules slowly changed the structure of diclofenac-Na (and/or that of the polymer) and a more stable arrangement of the molecules was formed, possibly involving first or second-order bonds between the API and the polymer. However, at the moment, we do not have more detailed knowledge concerning the nature of this transformation.

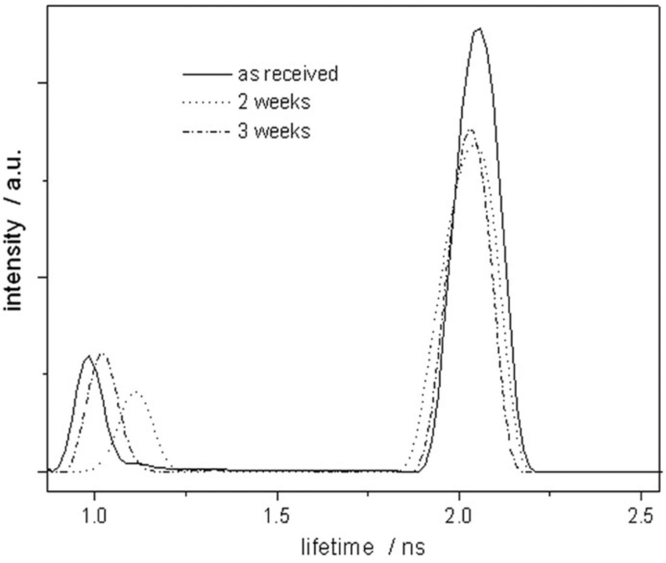

Fig. 2. *o*-Ps lifetime distributions in Sample 1 films. The extra peak (lifetime component) at around 1 ns indicates a significant relaxation of the polymeric chains during storage, due to water uptake.

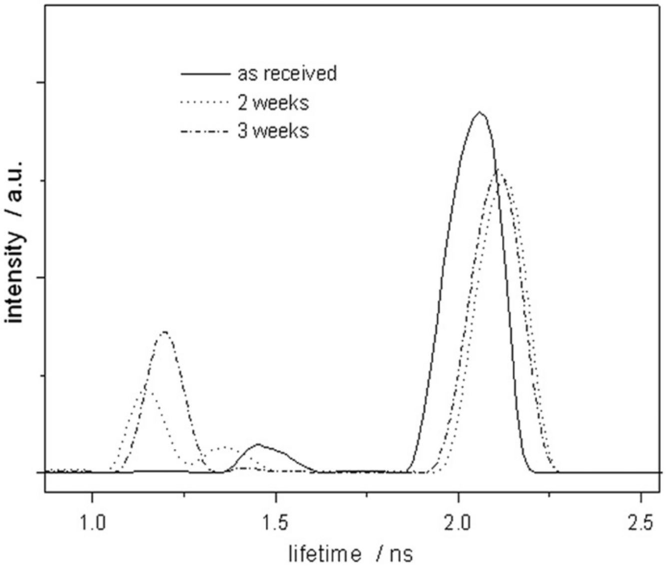

Fig. 3. *o*-Ps lifetime distributions in Sample 3 during the storage period. The relaxation is clearly shown by the peak(s) at around 1.25 ns.

4. Conclusions

A metastable structure is formed during the preparation of Eudragit® L 30D-55 films containing diclofenac-Na. This metastable structure slowly relaxes during storage. Indications were observed that a structural (and/or chemical) transformation takes place around the API molecules.

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VII

Research Article

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Physicochemical testing of free films containing non-soluble components

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Eudragit® L 30D-55 films containing diclofenac sodium in different concentrations (0%, 1%, and 5%) were studied by conventional physicochemical methods and positron annihilation spectroscopy. Diclofenac sodium was found to change the properties of the film formed significantly. Positron annihilation spectroscopy was applied to track the Eudragit–diclofenac interaction. The presence of diclofenac initially led to significant distortion of the structure of the pure Eudragit film. However, during storage (17°C, 65% relative humidity), the distorted structure relaxed because of water uptake from the air. At the end of the storage period, the free-volume size was almost the same in all films. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: free films; breaking strength; positron annihilation spectroscopy

INTRODUCTION

Active pharmaceutical ingredients (APIs) incorporated in film layers have become very common in recent years. Such products can be divided into two groups: mucoadhesive films, where the API is absorbed from the buccal mucosa in order to achieve a local (e.g. antibacterial) or a rapid systemic effect, avoiding the first-pass effect, and preparations (tablets, granules, pellets, etc.) in which the API is processed during coating. During the preparation of a coating layer, it is necessary to know its physicochemical properties, e.g. its glass transition temperature, minimal film-forming temperature (MFFT), flexibility and surface properties, how the API particles are located in the structure of the film-forming polymer, and whether these particles modify the properties of the film formed. The presence of insoluble particles in the coating liquid can modify the resulting film.[1,2] The APIs in the film layer are mostly in suspended form and rarely in dissolved form; the particle size of the API is therefore crucial, and the use of microcrystalline forms is recommended. In the present study, the aim was to prepare free films containing an API and to investigate the previously mentioned properties by conventional physicochemical methods and by positron annihilation spectroscopy (PALS). This latter method provides information on the size of free-volume holes in an amorphous material and on the structural changes in a polymer.

MATERIALS AND METHODS

Eudragit® L 30D-55 (Evonik Röhm GmbH, Pharma Polymers, Darmstadt, Germany) is an aqueous dispersion of anionic polymers with methacrylic acid functional groups. The coating liquid compositions contained titanium dioxide, talc, triethyl citrate (the suggested ratio for Eudragit® L [Eudragit brochure]), dimethicon (type E1049, a gift from EGIS Pharmaceuticals PLC, Budapest, Hungary) as antifoaming agent, and microcrystalline diclofenac sodium (Amoli Organics Pvt. Ltd., Mumbai, India) in different proportions as API. Table 1 presents the compositions of the samples.

Preparation of samples

The solid content of each coating dispersion was 20%. The first step is the preparation of the pigment suspension (Eudragit brochure). Conventionally, intensive homogenization of the materials (glidants, pigment, plasticizers, and other excipients, including the API) in water must be performed with a high-speed apparatus. After this, the homogeneous pigment suspension must be gently mixed with the polymer dispersion to prevent coagulation. The pigment suspension containing 0%, 1%, or 5% of the API was prepared by Ultra-Turrax (IKA-Werke GmbH & Co. KG, Staufen, Germany) mixing (17 500 rpm) for 10 min. After this, the suspension was poured into the polymer dispersion and mixed with an overhead stirrer (IKA-Werke GmbH & Co. KG) at 210 rpm for 15 min. As the final step, the mixture was sieved. The ready coating liquid was tested with an MFFT apparatus.

The free films were prepared by pouring the mixture onto a Teflon surface and drying it at room temperature (24 ± 1°C, 37% relative humidity [RH]) for 48 h. Deformation tests were performed 1 day after preparation. Ten to 12 mg samples of the cast films obtained and the API were used for differential scanning calorimetry (DSC) analysis. These films were also tested by PALS after various storage periods (1, 2, or 3 weeks at 17°C and 65% RH). Other free films were formed on a glass surface

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Table 1. Compositions of the samples

		Sample 1 (g)	Sample 2 (g)	Sample 3 (g)
I	Diclofenac sodium	0.00	1.00	5.00
	Talc	6.56	6.49	6.23
	Titanium dioxide	1.79	1.77	1.70
	Triethyl citrate	1.31	1.30	1.24
	Dimethicon	0.34	0.33	0.32
	Purified water	28.34	28.05	26.92
II	Eudragit® L 30D-55	33.34	33.00	31.67
	Purified water	28.34	28.05	26.92

and dried under the same circumstances. These free films were tested with an OCA 20 optical contact angle-measuring instrument (DataPhysics Instruments GmbH, Filderstadt, Germany). DSC and thermogravimetric (TG) analyses of the API were also performed.

Minimal film-forming temperature

To study the MFFT of the coating liquid, a Rhopoint MFFT apparatus (Rhopoint Instruments Ltd., Bexhill-on-Sea, UK) was used. The MFFT is the lowest temperature at which a latex, emulsion, or adhesive will uniformly coalesce when laid on a substrate as a thin film. An accurate MFFT value allows the formulation of products that cure correctly under specified application conditions. Three parallel tests were performed on each sample.

Deformation process

A breaking hardness tester was used to evaluate the deformation (breaking) process of the free films. The apparatus and the software were developed at the Department of Pharmaceutical Technology (University of Szeged). The apparatus contains a special specimen holder and a jowl and is connected to a computer via an interface. Thus, not only can the ultimate deformation force be measured, but the process (force–time and force–displacement curves) can also be followed. The film is located horizontally on a special ring, and the jowl moves vertically. If the measured plot (force–time) is parallel to the x-axis, the deformation is viscoelastic; if the plot rises linearly, the deformation is elastic. Parallel tests were carried out.

Contact angle measurements

The wetting process of free films was observed with an OCA 20 optical contact angle measuring instrument. The liquids were dispensed through a microsyringe. To investigate the changes in surface energy, diiodomethane (drops between 2 and 3 µl) was used together with purified water. Data were collected and analyzed with SCA (software of contact angle) instrumental software and also Microsoft Excel. The interactions of the drops with the surface were monitored with a CCD camera, with a time step of 1 s between successive acquisitions. The measuring accuracy of the video system was ±0.1. The contact angles reported are based on the averages for 10 static drops in different areas on the surfaces of the films, and 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).[3]

In the method of Wu, the SE is taken as the sum of dispersive (*d*) and polar (*p*) components. The SEs of solid materials can be determined by means of contact angle measurements on two liquids with known polarities. They can be assessed by solving two equations with two unknowns (eqn (1)):

$$(1+\cos\Theta)\,\gamma_1=\frac{4\left(\gamma_s^d\gamma_1^d\right)}{\gamma_s^d+\gamma_1^d}+\frac{4\left(\gamma_s^p\gamma_1^p\right)}{\gamma_s^p+\gamma_1^p} \tag{1}$$

where Θ is the contact angle, γ_s is the solid SE, and γ_l is the liquid surface tension.

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. The spreading coefficient of the coating liquid over the API (S_{12}) and that of the API over the film layer (S_{21}) can be determined according to eqns (2) and (3):[4]

$$S_{12}=4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d}+\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}-\frac{\gamma_1}{2}\right] \tag{2}$$

$$S_{21}=4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d}+\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}+\frac{\gamma_1}{2}\right] \tag{3}$$

The work of adhesion and the SE may be calculated from each other.[5,6] According to Dupré,[7] the work of adhesion ($\Delta\gamma_a$) describes the work necessary to separate two phases so that two new surfaces of unit area are formed but from different materials. The work input must compensate for the SEs (γ_{s1} and γ_{s2}) of the new surfaces. However, through the separation of the solid–solid interface, the work is lowered by the interfacial energy ($\gamma_{s1,s2}$) as in eqn (4):

$$\Delta\gamma_a=\gamma_{s1}+\gamma_{s2}-\gamma_{s1,\,s2} \tag{4}$$

The work of adhesion (W_a) is equal numerically to the energy that arises when two surfaces come into contact eqn (5):

$$W_a=4\left[\frac{\gamma_d^A\gamma_d^B}{\gamma_d^A+\gamma_d^B}+\frac{\gamma_p^A\gamma_p^B}{\gamma_p^A+\gamma_p^B}\right] \tag{5}$$

Differential scanning calorimetry

The DSC curves of the free films were studied with a Mettler-Toledo GmbH, Switzerland DSC 821^e instrument (Budapest, Hungary). The start temperature was 25°C, the end temperature was 300°C, and the heating rate was 10°C/min. After the end temperature was reached, the samples were refrigerated to 25°C and reheated to 300°C. An argon atmosphere and aluminum pans were used.

Thermogravimetry

The TG curves of the API were studied with a Mettler Toledo instrument. The method used for DSC was applied.

Positron annihilation spectroscopy

Positrons are the antiparticles of electrons. In polymers, a large proportion of injected positrons form a bound state with electrons before their annihilation.[8] One of the bound states, the *ortho*-positronium atom or *o*-Ps, lives long enough for its surroundings to be scanned. Moreover, according to a simple model, the lifetime of an *o*-Ps atom depends on the size of the free volume in which it is located (eqn (6)):[9]

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R+\Delta R} + \frac{1}{2\pi}\sin\left(\frac{2\pi R}{R+\Delta R}\right)\right]^{-1} \qquad (6)$$

where τ is the lifetime of the *o*-Ps, R is the radius of the (expectedly) spherical free-volume holes, and ΔR is a constant. The equation indicates that the lifetime of *o*-Ps atoms increases with the size of the free-volume holes in the material. Thus, any change in the free volume is reflected in the *o*-Ps lifetime.[10]

Positrons have been used for the study of free volume in polymers widely. Nowadays, by the improvement of the technique, they are reliably used in more and more sophisticated systems, i.e. in polymers containing plasticizer, variable amount of crystalline phase, and even in polymer composites.[11–13]

Positron lifetime measurements

The positron source applied for the measurements was made of carrier-free ^{22}NaCl. The active ^{22}NaCl was sealed between two very thin (5 µm) titanium foils, which ensured that 90–95% of the emitted positrons penetrated the studied polymer samples. The activity of the source was about 4×10^5 Bq.

Positron lifetime spectra were recorded with a fast–fast coincidence system.[14] The system was constructed from standard ORTEC electronic units, and the detectors were made from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps.

The lifetime spectra were evaluated, and lifetimes were extracted from them by means of the RESOLUTION (Computer Installation, National Laboratory, Roskilde, Denmark) computer code.[15] In every case, three lifetime components were obtained without any constraining of the parameters, the longest of them characterizing the *o*-Ps annihilation. As this is the most reliable parameter of lifetime spectra in the case of polymers, we use this parameter alone to characterize Eudragit L films.

It should be noted that, as the titanium foil sealing the positron source excludes Ps formation in the source, any Ps signal originates from the sample. Thus, we did not have to apply the code POSITRONFIT[15] to account for source corrections. By this, we have lost the possibility for interpreting the two short lifetime components, but the *o*-Ps data have not been affected in any respect.

RESULTS AND DISCUSSION

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 mechanical strength and the deformation of the free films can be described by deformation (breaking) curves (Fig. 1). These curves showed that these free films first undergo a viscoelastic deformation, which is followed by an elastic section, at the end of which breaking occurs. (Other polymers showed nearly the same behavior.[16–19]) Together with the increase in the content of the API, the strength of the films and the work of breaking (which can be calculated from the area under the curve) decreased significantly (Table 2). This means that the resistance and the processibility of the films were reduced. 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.

Besides the deformability, a knowledge of the surface properties of the polymer films is very important. SEs were calculated to describe the wetting process of the free films and the API (Table 3). Contact angles detected at 7 s were used for the evaluations. The SEs were much higher than those of the bulk film. 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 and the polar part of SE, the polarity and the work of adhesion increased, but the spreading coefficient ($S_{1/2}$) 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 $S_{1/2}$ 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.

Another important property is the thermoanalytical behavior of a film that contains non-soluble components. The thermograms of different cast films just after their preparation are presented in Fig. 2.

In the initial section (on the first heating), a glass transition can be seen for all the films (Table 4). The midpoint is shifted to a higher temperature level, and the range of the glass transition (onset–endpoint) is also increased in the cases of 1% and 5% API contents. The TG curves of the API showed that 6.1% of the API was lost in the first section (up to 300°C), and 18% of the API was lost in the first two sections.

In the third section (the reheating phase), a glass transition was detected for API content of 0% and 1%. These T_gs were shifted, and the range was also increased (Table 5). 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 the rearrangement of the macromolecules.

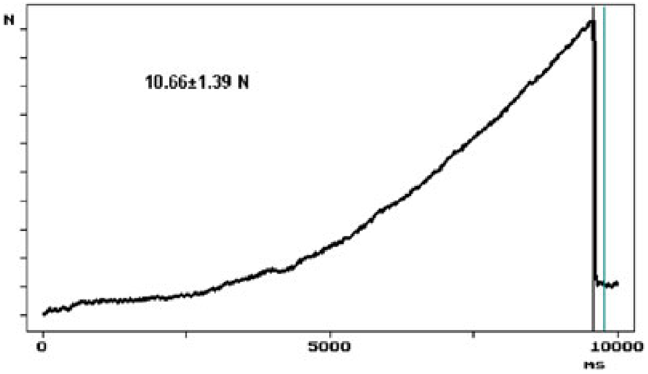

Figure 1. Deformation curve of free film containing no active pharmaceutical ingredient.

Table 2. Strength and thickness of free films

	API (%)	Breaking force (N)	Work of breaking (mJ)	Thickness (mm)
Sample 1	0	10.66 ± 1.39	36.62 ± 11.57	0.223 ± 0.022
Sample 2	1	5.75 ± 1.05	19.50 ± 17.72	0.212 ± 0.015
Sample 3	5	2.85 ± 0.51	15.05 ± 5.33	0.321 ± 0.030

API, active pharmaceutical ingredient.

Table 3. Surface free energies

	Sample 1	Sample 2	Sample 3	API
SE (γ)	55.34	61.0	70.95	80.3
Dispersive (γ^d)	37.87	39.4	38.44	43.57
Polar (γ^p)	17.47	21.61	32.51	36.73
Polarity (%)	31.57	35.43	45.82	45.74
$S_{1/2}$ (film on API)	17.72	15.18	8.77	—
$S_{2/1}$ (API on film)	−32.2	−23.42	−9.93	—
W_a	128.40	137.18	150.67	—

API, active pharmaceutical ingredient; SE, surface free energy.

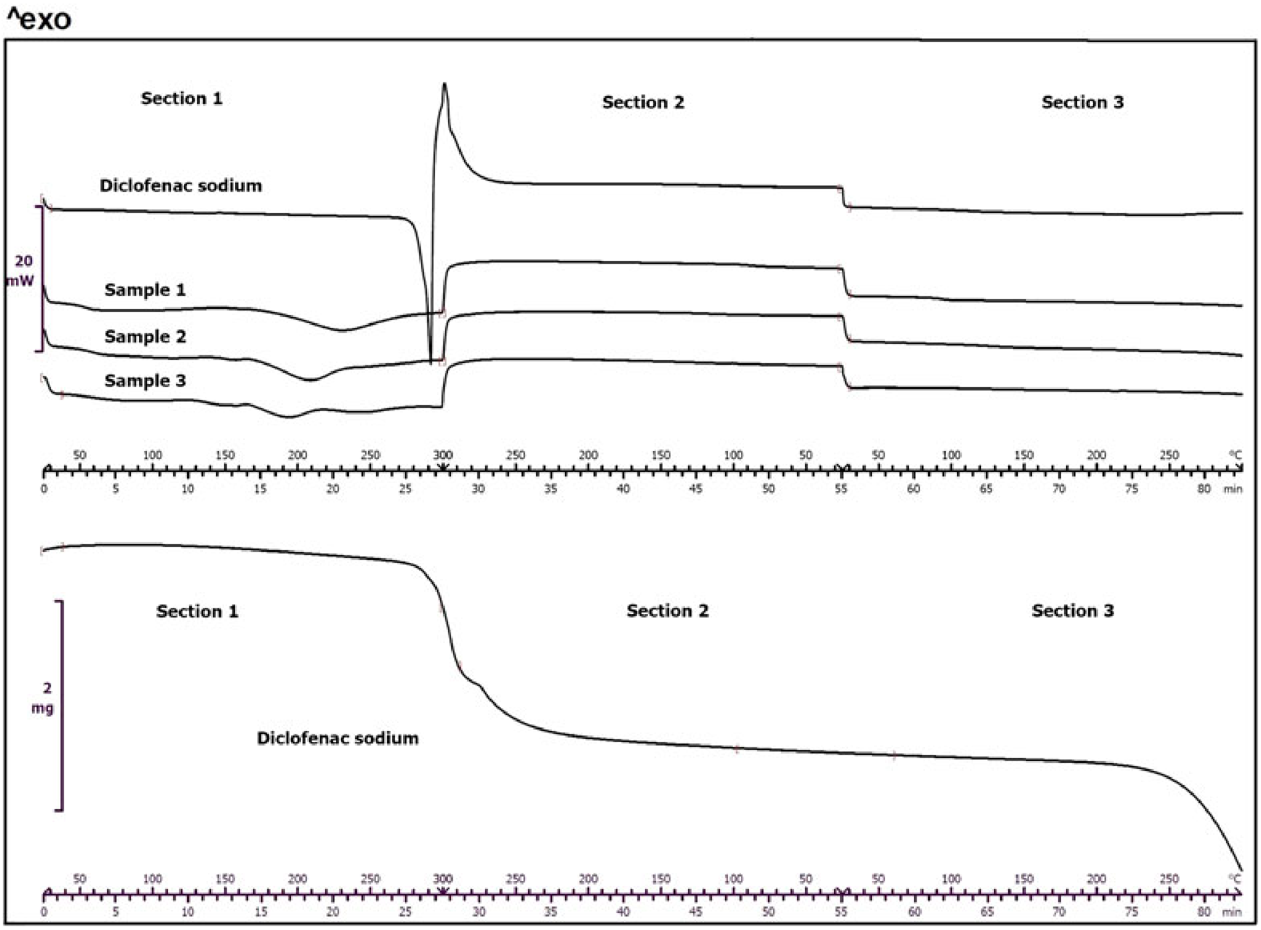

Figure 2. Differential scanning calorimetry and thermogravimetric curves.

Table 4. Data on glass transition in the first section of the differential scanning calorimetry curves

	API concentration		
Data	0%	1%	5%
Onset (°C)	49.98	51.85	45.75
Midpoint (°C)	56.16	59.11	63.5
Endpoint (°C)	60.21	64.26	73.13
Midpoint DIN (°C)	55.05	58.04	59.06
Delta cp DIN (J/g K)	0.373	0.409	0.45

API, active pharmaceutical ingredient.
DIN, Deutsche Industrie Normen.

Table 5. Data on glass transition in the last section of the differential scanning calorimetry curves

	API concentration	
Data	0%	1%
Onset (°C)	87.85	116.4
Midpoint (°C)	93.94	127.18
Endpoint (°C)	99.2	134.69
Midpoint DIN (°C)	93.43	125.52
Delta cp DIN (J/g K)	0.17	0.16

API, active pharmaceutical ingredient.
DIN, Deutsche Industrie Normen.

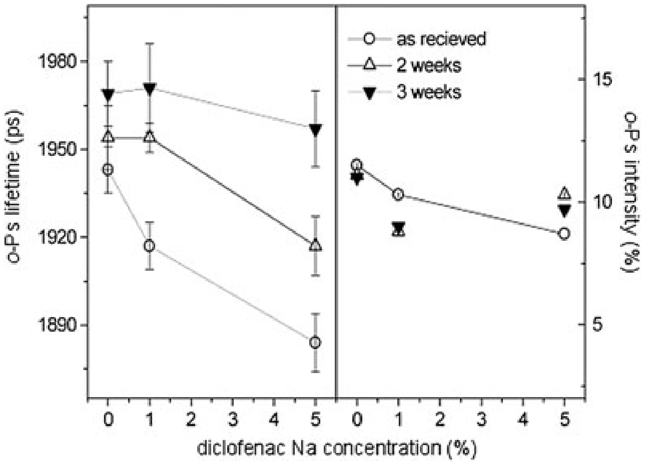

Figure 3. *Ortho*-positronium (*o*-Ps) lifetime and intensity as functions of diclofenac Na concentration in the studied films.

This internal structure and the free volume of the pores were tested by means of PALS. This measurement is very useful in the test of inner structure of polymers.[20,21] It can be seen in Fig. 3 that the *o*-Ps lifetime is decreased by the presence of API in the films, whereas the intensity of formation of the *o*-Ps atoms remains more or less the same. The average size of the free-volume holes, according to eqn (6), is decreased from $R = 4.46$ Å to $R = 4.41$ Å. 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 film formation, diclofenac occupies sites between Eudragit chains and thereby distorts the original structure. The distortion leads to the formation of smaller free-volume holes. Around the API molecules, a less flexible, denser polymer structure is formed, as it is reflected by the decreasing value of *o*-Ps lifetime.

During the storage period, the film absorbs water molecules from the air. The plasticizing effect of these water molecules promote relaxation of the distorted structure, and after 3 weeks of storage, all the films have a very similar structure. The average size of the free-volume holes is around 4.48 Å in every case. However, all the experimental results are consistent with our assumptions; further investigations are under way to verify this theory.

CONCLUSIONS

All in all, it can be concluded that non-soluble particles influenced the mechanical strength of the free films. On the increase of the amount of API in the free films, SE and the polar part of SE, the polarity and the work of adhesion increased, whereas the spreading coefficient decreased. The DSC curves revealed that all the samples exhibited a glass transition in the first section, but in the third section, sample 3 had no glass transition in contrast with samples 1 and 2, which can be explained by the disturbing effect of the crystals in the film structure. Free-volume holes were defined by PALS, where the presence of the API resulted in a decrease in the size of the free-volume holes. This decrease could be attributed to the effects of diclofenac on the structure of the films. The decrease subsequently vanished as the film absorbed water from the air and the structure relaxed because of the plasticizing effects of these water molecules.

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VIII

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Optimization of preparation of matrix pellets containing Eudragit® NE 30D

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ABSTRACT

Matrix pellets containing Eudragit NE 30D were produced by extrusion–spheronization, where the critical control points of the process were detected by means of a factorial design. The factors were the quantity of water, the dosing speed, the spheronization speed and the duration of spheronization. The breaking hardness and aspect ratio were measured and the significant factors were determined. On the basis of the results, a new combination of factors was used, which resulted in matrix pellets with the best characteristics.

Keywords: Extrusion; Spheronization; Formulation; Morphology; Pharmaceuticals; Polymers

1. Introduction

Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications (Ghebre-Sellassie, 1989). Interest in pellets as a dosage form (filled into hard gelatin capsules or compressed into disintegrating tablets) has increased continuously as their multiparticulate nature offers important pharmacological and technological advantages over conventional single-unit solid dosage forms (Bechgaard and Hagermann, 1978; Follonier and Doelker, 1992; Krämer and Blume, 1994; Ghebre-Sellassie and Knoch, 2002).

Several methods are applicable for pellet preparation, the most popular being solution/suspension layering, powder layering, direct pelletization with the use of high-shear mixers and conventional or rotary fluid-bed granulators, and extrusion–spheronization. These pelletization techniques have been reviewed in detail in a number of papers (Ghebre-Sellassie and Knoch, 2002; Erkoboni, 2003; Kleinebudde, 1997; Kleinebudde and Knop, 2007; Trivedi et al., 2007).

As this survey focuses on the extrusion–spheronization process, this multistep technique is briefly outlined below. Furthermore, extrusion refers only to wet extrusion; melt extrusion and solid-lipid extrusion are not considered. This process involves several distinct preparation phases: a uniform powder mixture of drug and excipient(s) is wet-massed by the addition of a liquid binder, followed by pressing of the moistened mass through an extrusion screen (extrusion) to form cylindrical extrudates, which are subsequently broken into smaller cylindrical rods and rounded into spherical granules by means of a fast-rotating friction plate (spheronization) and finally dried. This process is an efficient technique for the manufacturing of pellets (even for formulations with a high drug load), and allows a high throughput based on the continuous nature of the extrusion process when combined with multiple spheronizers operating in parallel or in series. A comprehensive review of this technique (Trivedi et al., 2007) details the different steps of the process and the effects of the different process parameters on the pellet quality at each stage of the extrusion–spheronization process.

In view of the specific nature of this process, not all moistened powder mixtures can be successfully extruded and spheronized. Newton (2002) defined the specific requirements for a wetted mass to be suitable for extrusion and spheronization, based on the pioneering papers of Reynolds (1970) and Conine and Hadley (1970). To allow extrusion, a cohesive plastic mass must be formulated that remains homogeneous during extrusion. The mass must possess inherent fluidity, permitting flow during extrusion, and self-lubricating properties as it passes through the die. The resultant strands of extrudates must not adhere to each other, and must exhibit plasticity so that the shape imposed by the die is maintained.

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The requirements for spheronization of the cylindrical extrudate are as follows: (a) the extrudate must possess sufficient mechanical strength when wet, yet it must be brittle enough to be broken down to short lengths in the spheronizer, but not so fragile that it disintegrates completely; (b) the extrudate must be sufficiently plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate in the spheronizer; and (c) the strands of the extrudates must not adhere to each other so that the particles do not aggregate during spheronization (Newton, 2002).

In relation to the above-mentioned requirements of the wetted mass, microcrystalline cellulose (MCC) is incorporated in most formulations that are processed via extrusion–spheronization, since it provides the wetted mass with appropriate rheological properties (Newton, 2002) for successful extrusion and spheronization (Shah et al., 1995). Its good binding properties make MCC the gold standard as an extrusion–spheronization aid, providing cohesiveness to a wetted mass containing MCC. Furthermore, it is able to absorb and retain a large quantity of water due to its large surface area and high internal porosity (Sonaglio et al., 1995), thereby facilitating extrusion, improving the wetted mass plasticity and enhancing spheronization. Moreover, by controlling the movement of water through the plastic mass, it prevents phase separation during extrusion or spheronization (Fielden et al., 1992). As a consequence of these properties, MCC-based pellets produced via extrusion–spheronization exhibit good sphericity, low friability, high density and smooth surface properties. Furthermore, from a processing aspect, relatively wide ranges of water content and processing parameters can be employed to provide pellets with acceptable quality, as an indication of the robustness of the formulations.

Various pharmaceutical excipients can be used to modify the liberation of an active agent from the pellets formulated by extrusion and spheronization. These components form a matrix system, which ensures appropriate liberation. Different types of polymers can be used to form soluble or insoluble systems. Their properties and the interactions between the components influence the dissolution of the active pharmaceutical ingredient. The film formation in the solid polymer matrix significantly influences the texture of the dosage form and hence the liberation of the active agent.

EUDRAGIT® NE 30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate that is highly suitable for sustained-release film coatings (El-Malah and Nazzal, 2008). and for sustained release granules (Bauer et al., 1998; Krajacic and Tucke, 2003). It is insoluble in water, displays low permeability and pH-independent swelling, and is highly flexible (Eudragit Brochure).

Our primary aim was to develop a matrix pellet filled in a hard gelatin capsule as a multiunit dosage form. This means a controlled drug-release formulation. The objective is to achieve a longer-lasting therapeutic effect with a medication that does not need to be taken as often and has fewer side-effects. These factors improve patient compliance and the safe administration of the medication, making the therapy more successful, especially for long-term regimens. With sustained release dosage forms, the phase that determines the rate is the precisely controlled drug release, not the absorption phase. When a rapid increase of the plasma level of the drug is desired, the drug is preferably separated into immediate and maintenance doses.

Table 1 – Composition of powder mixtures.

Components	Quantity (g)
Microcrystalline diclofenac sodium	50
Avicel PH 112	85

The reduced dosing frequency of sustained release dosage forms is generally accompanied by an increase of the single dosage of the drug.

2. Materials and methods

2.1. *Materials*

In the composition of the pellets, microcrystalline diclofenac sodium (Amoli Organics Pvt. Ltd.) was used as an active pharmaceutical ingredient (API), MCC (Avicel PH 112, FMC Corp., USA) and ethyl acrylate–methyl methacrylate copolymer (Eudragit® NE 30D Evonik GmbH, Germany) as binder and matrix-forming agents, and purified water as granulation liquid.

2.2. *Preparation of pellets*

The solid components of the powder mixtures (Table 1) were homogenized with a Turbula mixer (W.A. Bachofen, Basel, Switzerland) at 50 rpm for 10 min.

75 g of aqueous dispersion of polymer (Eudragit® NE 30D) was added manually to the mixture in a high-shear granulator with the same dosing speed as for purified water (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium) to prevent sticking in the pump. The mixture was moisturized further with a determined amount of purified water. The dosing speed and the amount of water were based on the data of the experimental design (Table 2). The dosing of water was carried out fractionally. The wet mass was kneaded with the following process parameters: impeller speed: 1500 rpm, chopper speed: 2000 rpm. The wet mass obtained was extruded by a mini screw (Caleva Ltd., Sturminster Newton, Dorset, UK) equipped with an axial screen with dies 1 mm in diameter and 4 mm in length, operating at 70 rpm. The jacked barrel of the extruder was cooled by water at 25 ± 2 °C. Each extrudate was collected in a container before it was spheronized. About 40 g of extrudate was spheronized at a time, on a spheronizer 12 cm in diameter (Model-120, G.B. Caleva Ltd., Sturminster Newton, Dorset, UK) fitted with a cross-hatch grooved plate. The time and speed of the spheronization were determined by the experimental design (Table 2). The pellets were dried under the same conditions, at 40 ± 2 °C for 24 h.

2.3. *Factorial design*

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,

Table 2 – Values of factors.

Factor	Low (−)	Zero (0)	High (+)
Quantity of purified water (X1)	60	70	80
Dosing speed (X2)	3	5	7
Speed of spheronization (X3)	750	875	1000
Duration of spheronization (X4)	10	15	20

Table 3 – Designation of samples.

	Quantity of Purified water (ml)	Dosing speed (ml/min)	Speed of spheronization (rpm)	Duration of spheronization (min)
P1	60	3	750	10
P2	80	3	750	10
P3	60	7	750	10
P4	80	7	750	10
P5	60	3	1000	10
P6	80	3	1000	10
P7	60	7	1000	10
P8	80	7	1000	10
P9	60	3	750	20
P10	80	3	750	20
P11	60	7	750	20
P12	80	7	750	20
P13	60	3	1000	20
P14	80	3	1000	20
P15	60	7	1000	20
P16	80	7	1000	20
P17	70	5	875	15

the speed of spheronization and the duration of spheronization. The 16 experimental set-ups supplemented with a central point are indicated in Table 3. The experiments were performed in randomized sequence, so as to eliminate systematic errors. The following approach, containing the interactions of the factors, was used to determine the response surface and the relative effects of the factors (*b*):

$$\begin{aligned} y = {} & b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 \\ & + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{123}X_1X_2X_3 \\ & + b_{234}X_2X_3X_4 + b_{124}X_1X_2X_4 + b_{134}X_1X_3X_4 \end{aligned}$$

Statistica for Windows 8.1 AGA software (StatSoft, Inc. Tulsa, USA) was used for the calculations. During the mathematical evaluations, the confidence interval was 95%, i.e. the differences were significant if $p < 0.05$.

2.4. *Morphological study*

The particle size and the shape of the pellet surface were studied with a stereomicroscope (Zeiss Stemi 2000-C, Carl Zeiss GmbH, Vienna, Austria). A Quantimet 500 (Q500MC) image processing and analysis system (Leica Cambridge Ltd., Cambridge, UK) was used. The aspect ratio was utilized for the evaluation of the shape of the particles. 500 pellets of each sample were checked.

2.5. *Mechanical properties of the pellets*

The breaking hardness was tested for pellets with diameters measuring between 1000 and 1250 μm. The strength tester and the software were developed in our institute. The tester contains a special specimen holder and a stamp, and is connected to a computer via an interface. The loading indicates some stress in the sample and it can deform. As the surface area of the jowl is constant, the stress deformation and force–time profiles are the same. Thus, not only can the ultimate deformation force be measured, but the process (force–time and force–displacement curves) can also be followed. The specimen is located horizontally on a special plate and the stamp moves vertically. If the measured plot (force–time) is parallel to the *x*-axis, the deformation is viscoelastic; if the plot rises linearly, the deformation is elastic. Twenty parallel measurements were performed.

The measurement range was 0–200 N, the speed of the stamp was 20 mm/min, and the output was 0–5 V. The sensor was a Unicell force measuring instrument, calibrated with the C9B 200 N cell.

2.6. *Dissolution tests*

Pellets (160 mg) were placed into the basket of a dissolution tester (Erweka DT 700, Heusenstamm, Germany). The dissolution medium consisted of phosphate buffer (pH 6.8), kept at 37.0 ± 0.5 °C for 4 h. The rotational speed of the baskets was set at 100 rpm. The dissolution system was combined with an automatic sampling station. Samples of 5 ml were withdrawn from the phosphate buffer medium at 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min. Absorbance was measured spectrophotometrically (Unicam Heλios Alpha, Spectronic Unicam, Cambridge, UK) at $\lambda_{max} = 276$ nm. Three parallel tests of dissolution were performed.

3. Results and discussion

The present work was focused on optimization of the shape and mechanical properties of pellets prepared by extrusion–spheronization. Table 4 displays the aspect ratios and breaking hardnesses of the different samples.

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. For all the samples, the deformation process (Fig. 1) could be divided into three phases: a short elastic part (1), followed by a plastoelastic phase (2), and finally an elastic section peaking (3) at the breaking point.

The similarity of the curves for the various samples suggests that the mechanism of deformation of the pellets is primarily based on the composition of the product and is only minimally affected by the parameters of the production process. Nevertheless, the breaking hardness of the products is significantly influenced by the process parameters (Table 5). The significant factors and linear interactions are highlighted in red; the level of significance was determined in *t*-tests.

Table 4 – Aspect ratio and breaking hardness.

	Aspect ratio	Breaking hardness (N)
P1	3	41.78 ± 8.27
P2	–	–
P3	3	53.13 ± 12.36
P4	3	32.74 ± 6.15
P5	3	48.03 ± 10.48
P6	–	–
P7	3	45.57 ± 10.54
P8	1.142 ± 0.08	44.38 ± 6.93
P9	3	47.41 ± 13.84
P10	–	–
P11	1.637 ± 0.35	53.17 ± 8.88
P12	1.183±0.11	32.79 ± 2.69
P13	3	49.91 ± 8.32
P14	–	–
P15	1.463 ± 0.29	45.82 ± 8.16
P16[*]	1.082 ± 0.04	**37.55 ± 5.24**
P17	3	47.83 ± 9.17

[*] The best product.

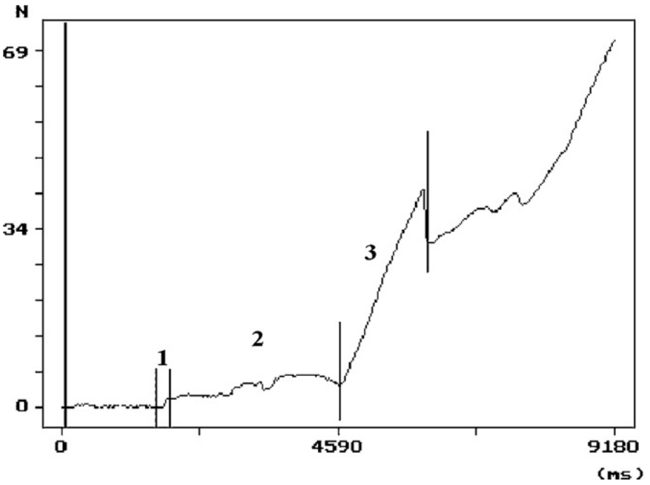

Fig. 1 – Curve of pellet deformation.

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, because the water acts as a plasticizing agent in the mixtures. 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. When a lower liquid feeding rate is used, the water can spread on the surface even of the small particles and can form an incompressible barrier during extrusion. This is the reason why compositions containing a high amount of water added at a low dosing speed cannot be extruded. At higher feeding rates, this effect is of less importance (Fig. 2): because of the shorter kneading time dry aggregates remain in the wet mass, which provides sufficient bonding of the particles during extrusion. This is a possible explanation of why the feeding rate has a positive effect on the mechanical properties of the pellets. This advantageous effect could be seen not only in the breaking hardness, but also in the deformability of the extrudates. Besides the duration of spheronization, the dosing speed and the linear interaction of the two factors exert significant effects on the shape of the pellets (Table 6). 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 (Fig. 3). The effects of the speed of spheronization and the quantity of water were not significant, but still considerable, which is important, because the data in Table 7 show that the aspect ratios of many samples were far from the ideal value. The aspect ratio was close to 1 in the case

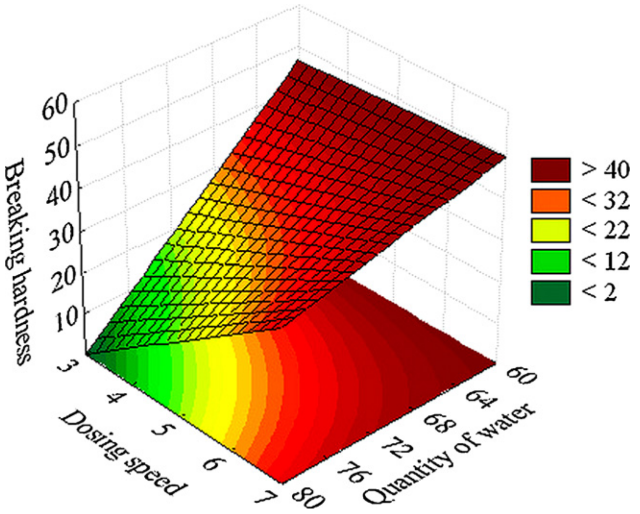

Fig. 2 – Effects of dosing speed and quantity of water on the breaking hardness of the pellets.

Table 5 – Effects of the parameters on the breaking hardness.

Var.:Breaking hardness

$R^2 = 0.98308$

	Effect	Std. err.	t(5)	*p*	Coeff.
Mean/Interc.	33.27	1.17	28.5153	0.000001	33.27
(1) quantity of water	−29.67	2.33	−12.7159	0.000053	−14.84
(2) dosing speed	19.75	2.33	8.4654	0.000378	9.88
(3) speed of spheronization	1.28	2.33	0.5486	0.606891	0.64
(4) duration of spheronization	0.13	2.33	0.0546	0.958539	0.06
1 by 2	17.11	2.33	7.3340	0.000739	8.5
1 by 3	2.82	2.33	1.2086	0.280855	1.41
1 by 4	−1.82	2.33	−0.7811	0.470103	−0.91
2 by 3	−0.91	2.33	−0.3889	0.713337	−0.45
2 by 4	−1.75	2.33	−0.7500	0.487020	−0.88
3 by 4	−1.30	2.33	−0.5582	0.600766	−0.65

Table 6 – Effects of the parameters on the shape of pellets.

Var.: Aspect ratio

$R^2 = 0.91254$

	Effect	Std. Err.	t(5)	*p*	Coeff.
Mean/Interc.	2.47	0.113	23.44626	0.000003	2.47
(1) quantity of water	−0.34	0.21	−1.59822	0.170887	0.17
(2) dosing speed	−1.06	0.21	−5.04035	0.003966	0.53
(3) speed of spheronisation	−0.27	0.215	−1.26587	0.261334	0.13
(4) duration of spheronization	−0.60	0.21	−2.83501	0.036459	0.30
1 by 2	−0.34	0.21	−1.59822	0.170887	0.17
1 by 3	−0.22	0.21	−1.05935	0.337912	0.11
1 by 4	0.13	0.21	0.60712	0.570282	0.06
2 by 3	−0.27	0.21	−1.26587	0.261334	0.13
2 by 4	−0.60	0.21	−2.83501	0.036459	0.30
3 by 4	0.20	0.21	0.93946	0.390624	0.10

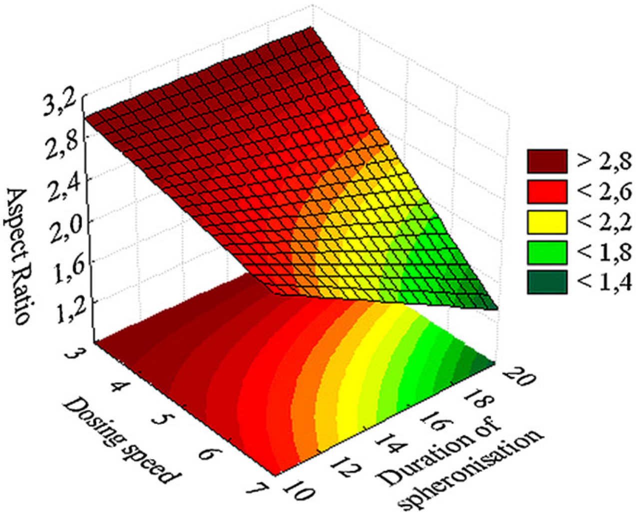

Fig. 3 – Effects of dosing speed and duration of spheronization on the aspect ratio of the pellets.

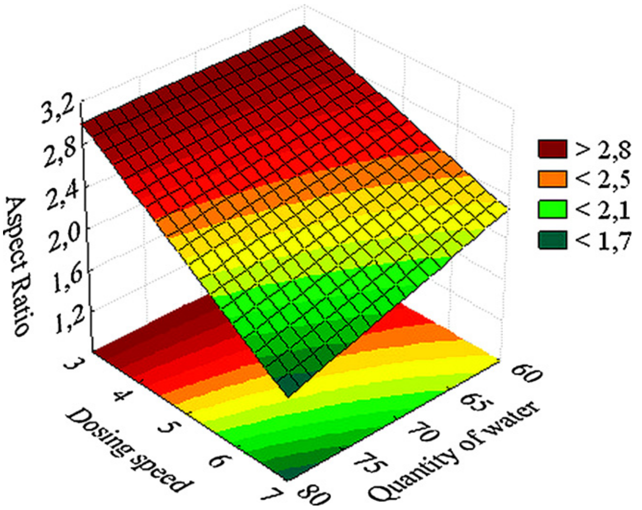

Fig. 4 – Effects of dosing speed and quantity of water on the aspect ratio of the pellets.

of Sample 12, but was best for Sample 16. It can also be seen, that the breaking hardness of this sample was very good. It is known that the shape can modify the breaking hardness of different systems (mainly for tablets) (Davies et al., 2007; van Santen et al., 2002). 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. To decrease the rate of aggregation the decreasing of the water quantity was necessary. Nevertheless, this will have a negative effect on the aspect ratio of pellets. 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. The calculations based on equation of response surface showed that the further change of the

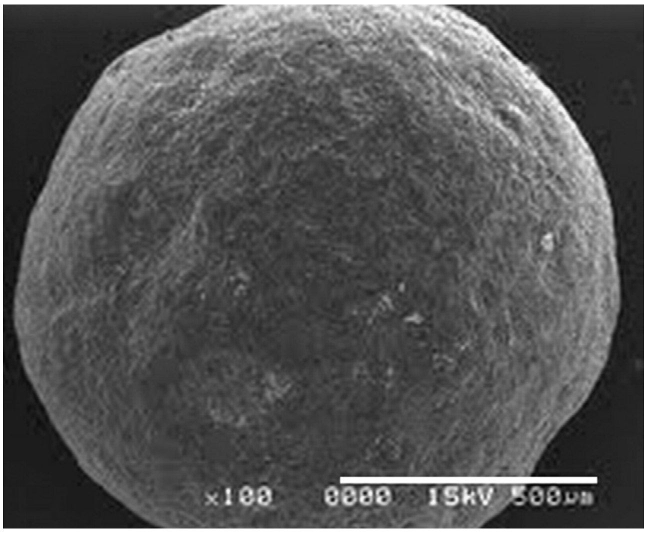

Fig. 5 – Surface of Sample 18 (SEM).

Table 7 – Manufacturing factors of the product.

	Quantity of Purified water (ml)	Dosing speed (ml/min)	Speed of spheronization (rpm)	Duration of spheronization (min)
Sample 18	62	9	1000	20

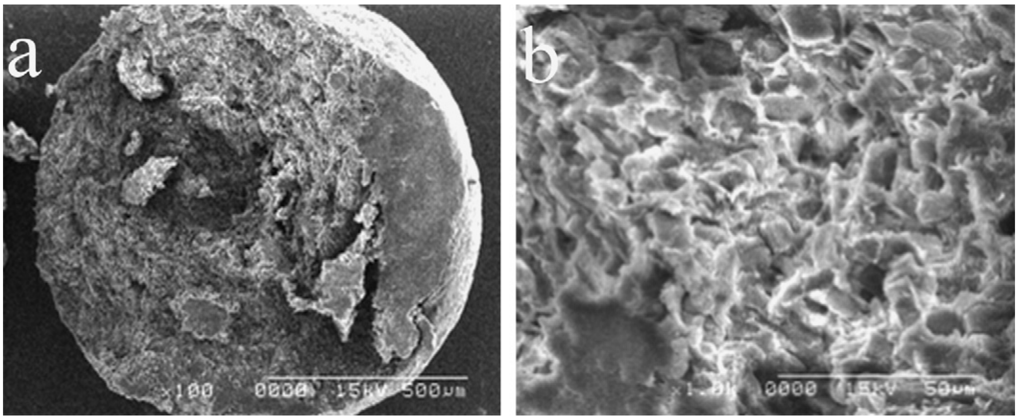

Fig. 6 – Cross-section of Sample 18 (SEM); magn. 100× (A), 1000× (B).

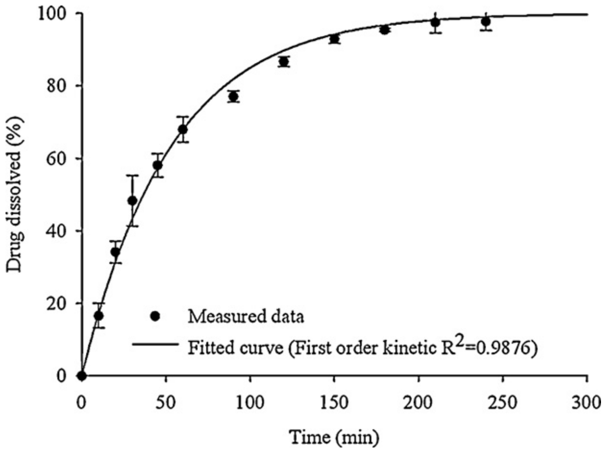

Fig. 7 – Dissolution rate of the drug of Sample 18.

conditions of spheronization will be not necessary, so they were kept in +1 level (Fig. 4).

On the basis of these considerations a new combination of factors (Sample 18) was applied (Table 7), where we achieved matrix pellets with optimized characteristics (aspect ratio: 1.083 ± 0.04, breaking hardness: 38.18 N ± 4.16).

In this case too, the impeller torque increased at the end of the process, but not as significantly as for Sample 16; and no large aggregates were formed.

The SEM picture reveals, that the surface of Sample 18 is smooth, without pores (Fig. 5). The cross-section picture demonstrates the compact texture (Fig. 6A), and at higher magnification it is clear that the particles formed a matrix system (Fig. 6B).

The physical parameters indicated that this sample was suitable for dissolution studies. The results showed, that 50% of the API had dissolved after 40 min, and about 85% after 240 min. The dissolution curve was of saturation type, following first-order kinetics (Fig. 7).

4. Conclusions

It can be concluded that Eudragit® NE 30-D 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 (pH = 6.8). This means that this product may be used as a delayed release dosage form.

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