University of Szeged
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Summary of Thesis

IMPROVEMENT OF THE SOLUBILITY AND DISSOLUTION RATE OF NIFLUMINIC ACID TO ACHIEVE RAPID DRUG RELEASE

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1. INTRODUCTION

Efforts to innovate existing medication include the development of medicines with higher selectivity of action, less toxicity and side-effects, higher stability, a more favourable pharmacokinetic profile and improved patient compliance. Modern pharmaceutical technology is concentrated on new drug forms which are targeted to the exact site at the appropiate time, with maximum efficiency and with reduced side-effects.

The solubility properties of drugs and the dissolution of the active substance from dosage forms have a basic impact on the bioavailability of the product. Generally, only the dissolved pharmacon is able to absorb and the dissolution rate greatly affects the rate of transport processes if the dissolution is the slowest step in the LADMER system. Enhancement of the solubility of poorly-soluble drug substances is one of the most important tasks in pharmaceutical technology. With new material drug carriers and new technological processes, it is possible to achieve this.

Complexation is one of several ways to favourably enhance the physicochemical properties of pharmaceutical compounds. It may loosely be defined as the reversible association of substrate and ligand to form a new species. Cyclodextrins (CDs) are classical examples of compounds that form inclusion complexes. These complexes are formed when a ”guest,, molecule is partially or fully incorporated into the cavity of a ”host,, molecule. When inclusion complexes are formed, the physicochemical parameters of the guest molecule are disguised or altered, and improvements in the solubility, stability, taste, safety and bioavailability of the molecule are commonly seen.

Pharmaceutical solid dispersion technology is generally accepted as a technique with which to enhance the dissolution characteristics of drugs with poor water solubility. For this purpose, the drug substance is dispersed in a water-soluble inert polymer matrix; at the higher surface area due to the presence of the polymer, sometimes the drug solubility and dissolution rate may increase.

This thesis is based on investigations of an anti-inflammatory drug nifluminic acid (NIF), with poor water solubility, to apply these technological procedures so as to increase its solubility and dissolution rate. *Iervolino* and co-workers applied CDs in 1:1 ratio, using three methods to reduce the gastric toxicity of NIF and could improve its safety profile. This thesis focused on the other possibilities of formulation of the drug**.**

2. EXPERIMENTAL AIMS

The aims of the present work were as follows.

In view of the poor water-solubility of a pharmaceutical ingredient, NIF, my aim was to increase its solubility and dissolution rate by applying different formulation methods.

The first aim of the study was to prepare *binary* and *ternary CD complexes* at several mole and mass ratios and via three complexation methods.

The second aim was to examine *solid dispersion systems* with solvent evaporation processes, such as vacuum- and spray-drying technologies.

The third aim was to investigate the characteristic physicochemical properties, biopharmaceutical behaviour for solubility, dissolution rate and structural characteristics of the samples on the basis of the following:

1. Preformulation studies on the products
   a. Recording the contact angles to establish their wettability
   b. Determination of the *n*-octanol/water partition coefficient to predict their permeability features
   c. Investigation of the saturation concentration in water to determine their solubility
   d. Analysis of the particle size
2. *In vitro* investigations
   a. Determination of the solubility and the rate of dissolution of the drug in simulated media
   b. Determination of the membrane diffusion
3. Structural evaluations
   a. Study of the *Fourier* transform-IR spectra, XRPD and thermal analysis (DSC and hot-stage microscopy (HSM))

3. MATERIALS

3.1. Active substance: Nifluminic acid (NIF)

NIF: 2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid
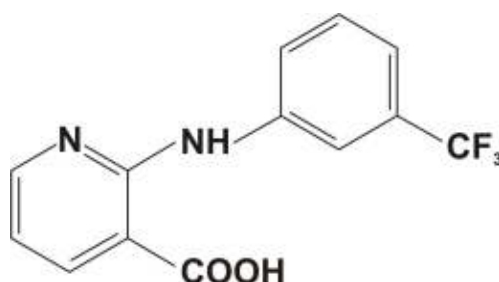(G. Richter Ltd., Hungary)
Chemical structure (see Fig. 1)

Fig. 1. Chemical structure of NIF

Molecular formula:	$C_{13}H_9F_3N_2O_2$
M_w:	282.23
Melting point:	205 ºC
Original name:	Donalgin®
Description:	a yellow, fine powder

NIF, an anthranilic acid derivative, is a frequently used anti-inflammatory drug, which also has a weak analgetic effect. It is primarily used to treat different forms of rheumatism, *e.g.* rheumatoid arthritis and arthrosis, and to decrease other inflammatory phenomena. The usual single dose is 250 mg of NIF for adults, generally in capsules (*e.g. Donalgin® capsule*, G. Richter Ltd., Budapest, Hungary). It has some side-effects, such as nausea or vomiting. In cases of stomach ulcer, it may only be used under medical control. Three h after a 250 mg dose administered to 6 male volunteers as the first dose on day 10 of a 14-day 250 mg, 4 times daily dosage regimen, the mean peak plasma concentration of radiolabelled NIF was 123 µg/ml. According to the BCS, NIF can be considered a class II compound, *i.e.* a water-insoluble, lipophilic and highly permeable compound. Since NIF is also widely prescribed for mild illnesses, the safety aspect becomes central and efforts should be made to optimize the overall drug pharmacological profile.

3.2. Auxiliary materials

- α-CD, β-CD, γ-CD, hydroxybutenyl-β-CD (HBU-β-CD), 2-hydroxypropyl-β-CD (HP-β-CD), heptakis-2,6-di-*O*-methyl-β-CD (DIMEB) and randomly methylated-β-CD (RAMEB) (Cyclolab R&D Laboratory Ltd., Hungary); Captisol® (Cydex, Inc., USA).
- polyvinylpyrrolidone (PVP): K-90, M_w: 1 300 000 (Pharmacopoeia Hungarica 7th Edition); C-30 ($M_w \sim 58\ 000$), K-25 ($M_w \sim 34\ 000$), C-15 ($M_w \sim 8\ 000$) (C/o ISP Customer Service GmbH, Germany)

- other chemicals, like acetone, ethanol, methanol are analitical purity (Spektrum 3D Ltd., Debrecen, Hungary).

4. METHODS

4.1. Preparation of the samples

4.1.1. Cyclodextrin binary complexes

The products were prepared in four different mole ratios (NIF:CD mole ratio = 2:1, 1:1, 1:2 and 1:3). *Physical mixtures* (**PMs**): The plain drug and CD were mixed in a mortar and sieved through a 100 μm sieve. Two types of solvent method were applied (kneading and ultrasonication). *Kneaded products* (**KPs**): **PMs** of the drug and HP-β-CD were mixed with the same quantity of a solvent mixture of ethanol + water (1:1). They were kneaded until the bulk of the solvent mixture had evaporated. The *ultrasonicated systems* (**USs**): the **PMs** were dissolved in 50 % ethanol, placed in the Grant ultrasonic bath XB2 (England) for 1 h, dried and pulverized. After this, they were dried at room temperature and then at 105 ^{o}C, and were pulverized and sieved through a 100 μm sieve.

4.1.2. Cyclodextrin ternary systems

The three-component products were prepared in four different mole ratios (NIF:HP-β-CD mole ratio = 2:1, 1:1, 1:2 and 1:3), in all cases containing 15% (w/w) PVP K-90. *Ternary physical mixtures* (**PMs+PVP**): NIF, HP-β-CD and PVP were mixed in a mortar and sieved through a 100 μm sieve. *Ternary kneaded products* (**KPs+PVP**): PMs+PVP were mixed with the same quantity of a solvent mixture of ethanol + water (1:1), and were kneaded until the bulk of the solvent mixture had evaporated. After this, they were dried at room temperature and then at 105 ^{o}C, pulverized and sieved through a 100 μm sieve.

4.1.3. PVP solid dispersions

The two-component products were prepared in four different mass ratios (NIF:PVP mass ratio = 1:1, 1:2, 1:4 and 1:6). The **PMs C-15, C-30** and **K-25** were mixed, pulverized in a mortar and sieved through a 100 μm sieve.

Solid dispersions were prepared by using a vacuum dryer and spray dryer for solvent evaporation. The *solvented products* were prepared with drug:PVP K-25 mass ratios of 1:1, 1:2, 1:4 and 1:6 (**SP K-25**). To a solution of NIF (1 g) in 30 ml of acetone, the appropriate amount of PVP K-25 was added. The minimum amount of methanol was added to solubilize the polymer. The solvents were removed under reduced pressure at 30 ^{o}C and the residue was dried under vacuum at room temperature for 3 h. The samples were pulverized and sieved through a 100 μm sieve.

The *spray-dried samples* (SPDs) were prepared by using a Büchi Mini Dryer B-191 (Switzerland), at 165 ^{o}C inlet and 86 ^{o}C outlet temperature with a compressed air flow of 600 l/min and a nozzle diameter of 0.5 mm as solvent evaporator. The aspirator rate was 80% and the pump rate was 10%. According to some references, the M_w of the polymer might play a role in the performance of a solid dispersion and better results can obtained with a lower M_w. However, at a higher ratio of PVP, the solubilization process may be neutralized by the diffusion process by increasing the viscosity of the solution around the particle. For these reasons, by the preparation of the spray-dried products were prepared in mass ratios of 1:5 and 1:10 with PVP C-15 (**SPD C-15**) – because of its low M_w – and were dissolved in 30% ethanol.

All of the products were stored under normal conditions at room temperature (22 ^{o}C).

4.2. Physicochemical characterization of the products

The OCA Contact Angle System (Dataphysics OCA 20, Dataphysics Inc., GmbH, Germany) was used for studies of the **wettability** of NIF and its products applying the circle fitting method.The powders were compressed under a pressure of 1 ton by a Specac hydraulic press (Specac Inc., USA).

The **partition coefficients** (K_p) of the samples were determined, which is defined as a ratio of drug concentration in the oil phase (usually represented by *n*-octanol) divided by the drug concentration in the aqueous phase measured at equilibrium under specified temperature *in vitro* in an oil/water two layer system.

Saturation concentrations of solid dispersion systems were determined at 25 °C. NIF and its products were added to distilled water during continuous stirring until the excess drug appeared in suspended form. After filtration, the saturated solution was diluted and the drug concentration was determined spectrophotometrically.

Particle size and distribution of solid dispersions were measured by LEICA Image Processing and Analysis System (LEICA Q500MC, LEICA Cambridge Ltd., England).

4.3. *In vitro* investigations

Dissolution profiles were investigated by USP dissolution apparatus (USP rotating-basket dissolution apparatus, type DT; in simulated gastric medium (SGM) (pH = 1.1 ± 0.1; 94.00 g of 1 M HCl, 0.35 g of NaCl, 0.50 g of glycine to 1000 ml with distilled water), and simulated intestinal medium (SIM) (pH= 7.0 ± 0.1; 14.4 g of $Na_2HPO_4·2H_2O$, 7.1 g of KH_2PO_4 to 1000 ml with distilled water) with modified paddle method and their UV spectra were recorded by Unicam UV2/VIS spectrometer, Unicam Ltd., England.

The following **mathematical models** were used to evaulate the results of the dissolution: *Zero-order model*, *First-order model*, *Higuchi model*, *RRSBW model*, *Langenbucher*, *Modified Langenbucher* and *$(Bt)^a$ model*.

***In vitro* diffusion studies** were performed from 100.0 mL of SGM or SIM to simulated plasma (SPL) (pH = 7.5 ± 0.1; 20.5 g of $Na_2HPO_4·2H_2O$ and 2.8 g of KH_2PO_4 to 1000 ml with distilled water) by Stricker's Sartorius apparatus (Sartorius-Membranfilter GmbH, Germany) where the artificial membrane was made of cellulose acetate (Schleicher & Schuell ME 29, Dassel, Germany: pore size 3 μm, diffusion surface 40 cm^2). The diffusion rate constant, K_d was determined.

4.4. Structural evaulation

Microscopic observations of morphological features and their changes during heating were carried out with a LEICA Thermomicroscope (LEICA MZ 6, Germany).

In **DSC measurements** applying Mettler Toledo DSC 821^e thermal analysis system with $STAR^e$ thermal analysis program V6.0 (Mettler Inc., Schwerzenbach, Switzerland) and argon was used as carrier gas, during the investigation.

FT-IR spectra were measured on an AVATAR 330 FT-IR apparatus (Thermo Nicolet, USA).

The physical state of the NIF in the different samples was evaulated by **X-ray powder diffraction (XRPD)**. Diffraction patterns were obtained on a Philips PW 1710 diffractometer.

5. RESULTS AND DISCUSSION

5.1. Investigation of cyclodextrin binary and ternary complexes

The *contact wetting angles* of NIF, HP-β-CD, PVP K-90 and their products were determined in the 5th sec, because of the lowest SD (Table I). The contact angle of NIF was 71.7 °, i.e. it is a very hydrophobic drug.

Table I. Wetting angles of NIF and its products						
	[°]±SD	[°]±SD	[°]±SD	[°]±SD	[°]±SD	[°]±SD
NIF	**71.3±3.2**					
HP-β-CD	18.5±1.6					
PVP K-90	35.4±7.6	**PM**	**KP**	**US**	**PM+PVP**	**KP+PVP**
2:1		30.4±4.5	40.9±0.6	42.3±4.6	30.7±0.7	42.3±6.7
1:1		29.0±1.3	32.6±1.5	34.6±1.2	29.9±0.1	36.6±2.1
1:2		24.8±2.2	25.2±2.3	27.0±2.0	28.7±1.3	30.0±2.0
1:3		26.4±2.2	25.8±1.7	25.4±1.1	35.4±2.5	31.6±1.6

The wetting angles of the investigated products in all cases lay between the values for CD and NIF. The investigation of the systems produced by the different preparation methods revealed that, with increasing HP-β-CD content, the contact wetting angles decreased (except for 1:3 PM+PVP and 1:3 KP+PVP). Usually the 1:2 and 1:3 ratios gave better results. To compare the results of wettability with *n*-octanol/water partition coefficient, in both study the 1:2 PM+PVP and 1:3 ratios for all methods shown similar tendency.

NIF has a high *partition coefficient* (**1810.80**), reflecting its poor water solubility and high affinity for *n*-octanol; its concentration in water at 22 °C is 26.75 μg/ml, while that in *n*-octanol is 48439.07 μg/ml. The *n*-octanol/water partition coefficients revealed that the water solubility increase was generally better for the ternary than for the binary systems. The best partition coefficient results were 25.51 for 1:3 US; 5.94 for 1:2 PM+PVP and 9.13 for 1:3 KP+PVP. The concentration of NIF in water could be increased even 15-fold (from 26.75 μg/ml to 422.03 μg/ml).

NIF has an acidic character, and its *dissolution* was therefore better in SIM (14.33 mg/100 mL at 120 min) than in SGM (9.92 mg/100 mL at 120 min). In SGM, the dissolution increased in proportion to the CD content in all of the KPs, where the 1:3 KP gave the best dissolution result; the solubility increase was 4.4-fold as compared with the pure drug. Similar phenomena were observed for KPs+PVP. Elevation of the HP-β-CD ratio exerted a slight influence in increasing the dissolution of PMs, USs and PMs+PVP in SGM. In these cases,

the dissolution was prolonged, the quantity of NIF dissolved increasing only gradually. In SGM, extensive dissolution did not occur and the dissolutions of the different products were nearly the same as compared with NIF. In SIM the saturation concentration was attained in 10–15 min. The maximum solubility increase (7-fold) was observed for the 1:1, 1:2 and 1:3 ternary KPs, while a 3-fold increase was found for the 1:1 PM+PVP. The ***kinetic parameters*** show very well that the dissolution was dependent on the preparation methods because in some cases the kneading method and the use of PVP led to significantly higher dissolution rates as compared with NIF, especially in SIM.

NIF has a 2.36 (10^{-3}) cm/min as of Kd value compared with the K_d values of the samples, which were improved. With increase of the ***diffused drug concentration***, the K_d values rose. The KPs+PVP showed the lowest K_d, 0.98, and for the USs a 2–3-fold rise was observed. For the binary products (PMs and KPs), on decrease of the amount of CD, K_d increased.

The ***DSC*** curve indicates that the melting point of NIF is at 203.81 $^{\circ}$C. To investigate the thermal properties of the systems, partial complexation is presumable in the cases of binary samples [the melting point decreased with increase of the CD concentration (190–180 $^{\circ}$C)] and amorphisation or total complexation was detected for ternary systems (NIF melting was not observed in the DSC curves of the PMs+PVP) - Fig. 2.
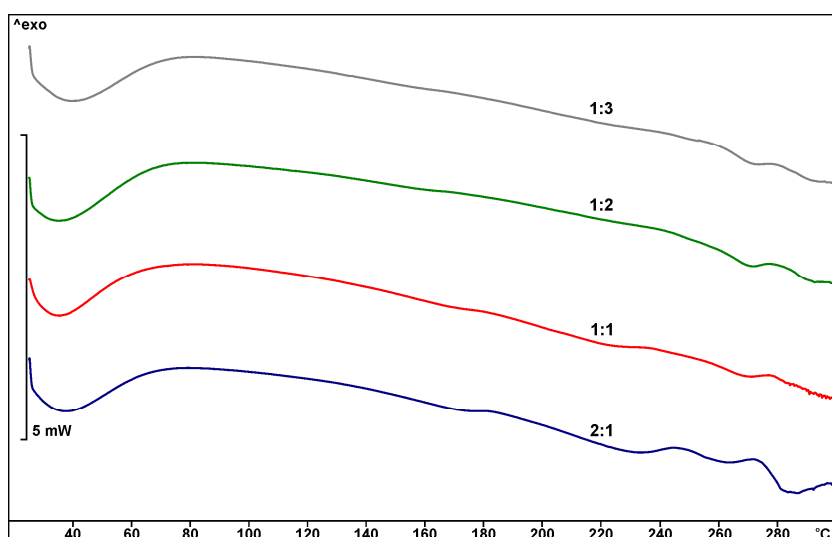

Fig. 2. DSC curves of PMs+PVP

5.2. Studies of solid dispersion systems

About 50 % of the *particles* of the SPs and SPDs had a particle size between 10–20 μm. Reduction of the length and width of the particles was significant for the 1:2, 1:4 SPs and 1:5 SPD (from ~ 46 μm to ~ 14 μm). According to the length's and width's reduction, the values of area and perimeter decreased significantly. This can result in an enhanced dissolution rate due to increases both in the surface area and solubilization.

The investigation of the *saturation concentration* presented that the concentration of NIF in water could be increased even 15-fold (from 26.75 μg/ml to 413.33 μg/ml). The water solubility of NIF in the PMs was improved 2–3-fold and that of the SPs 4–8-fold. The results were outstanding in the case of the SPDs, where an 11–15-fold solubility increase was observed. The *wetting angles* of the investigated products were in all cases decreased. The investigation of the systems produced by physical mixing revealed that, with increasing PVP content, the contact wetting angles decreased: the 1:6 products were wetted 2–3 times better than NIF itself. The solvent and spray-drying methods gave the best results, except for the 1:1 SP (7.5^{o}) and 1:5 SPD (26.3^{o}).

A maximum *solubility increase* of 3.5-fold was observed for the SPs, and of 8-fold for the SPDs in SGM. NIF alone yielded the slowest initial dissolution rate (Fig. 3).
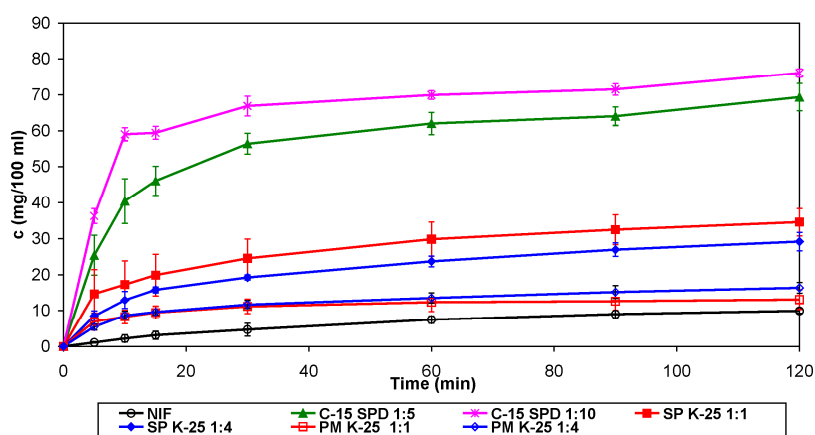

Fig. 3. Dissolution of NIF and different types of solid dispersions in SGM

All of the methods resulted in fast dissolution in SIM (Fig. 4). The saturation concentration was reached in 5–15 min. All of the solid dispersions resulted 100 % drug release in SIM while for the 1:4 and 1:6 PMs with PVP K-25 resulted 86 % drug release (for this reason, K-25 was chosen at the beginning to prepare the SPs).
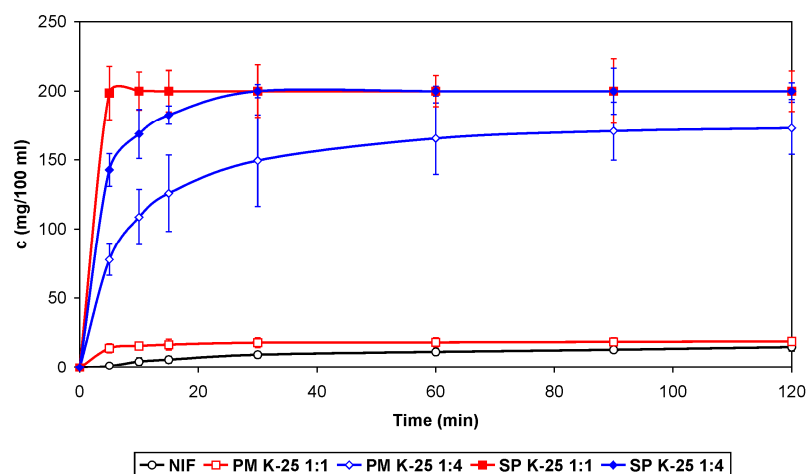
Fig. 4. Dissoultion curves of different types of solid dispersions in SIM

To monitor the ***dissolution rate*** of PMs in SIM, in all cases were lower, than the pure drug, except for the 1:4 and 1:6 PM K-25, where 15 and 21-fold. Dissolution rates for solid dispersions were significantly greater than those for PMs and NIF. In SGM 2.3−5.26-fold improvement were marked and in SIM 26−51-fold. PVP may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media.

For all the products except the SPs, the ***diffusion*** was more advantageous than that of NIF into SGM. The diffusions of the products were also avaluable in the case of SGM.
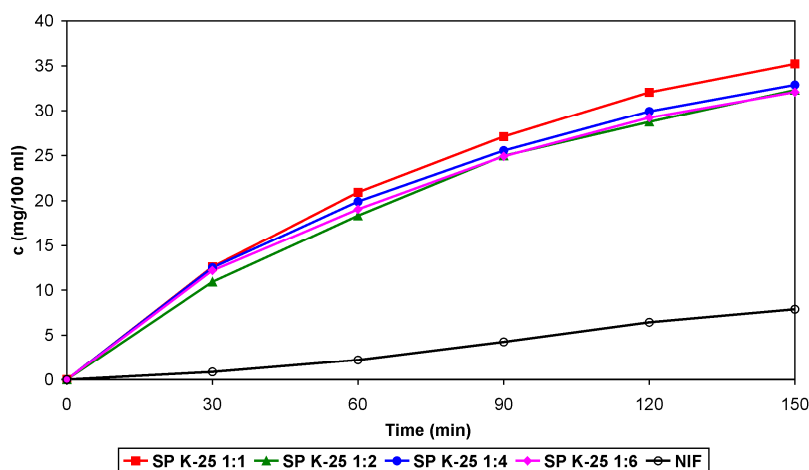

Fig. 5. Diffusion curves of NIF and SPs in SGM

As regards the PMs containing PVP, the diffusion from the 1:4 compositions exhibited a 2-fold increase after150 min. A 4.5-fold diffusion increase was measured for the SPs (Fig. 5) and a 2-fold improvement for the SPDs. The last part of the diffusion plots had a saturated character, as a consequence of the increased amount of diffused drug.

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The **DSC** curves did not reveal a melting peak for NIF in any of the solid dispersions. This may be due to the interaction between NIF and PVP in these systems. In contrast with the XRPD patterns of the PMs K-25 (without any amorphous character of NIF), the melting point of the drug was not observed. This indicated a NIF:PVP solid-state interaction induced by heating. The different **thermomicroscopic investigations** indicated that, for the PMs K-25, NIF was dissolved in the melted PVP. Changes in the PMs K-25 during heating were detected by HSM. The photographs in Fig. 6 demonstrate the morphology of PM K-25 in 1:1 ratio from the beginning of heating up to 160 $^{\circ}$C. With increase of temperature, the PVP began to melt, and above 130 $^{\circ}$C its melting was complete. It may be seen that the NIF particles were dispersed in the melt and subsequently dissolved with rising temperature. During heating, the drug particle size was steadily reduced, showing its dissolution in the PVP melt. The NIF was completely dissolved in the melt of PVP at close to 160 $^{\circ}$C, a temperature about 50 $^{\circ}$C lower than the melting point of the pure drug. This finding can explain the absence of any sign of melting in the DSC thermograms of the PMs K-25.
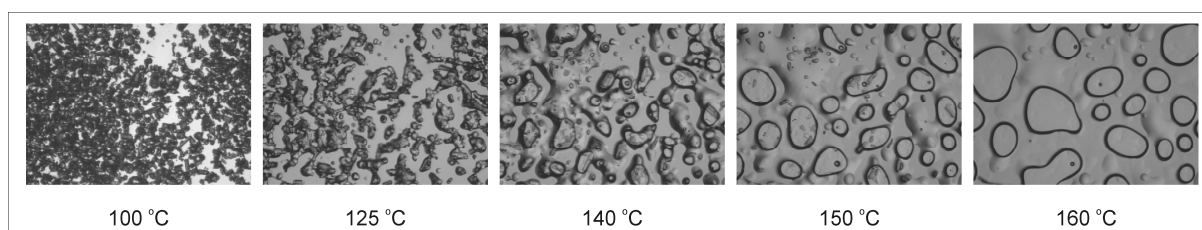

| 100 °C | 125 °C | 140 °C | 150 °C | 160 °C |

Fig. 6. HSM photographs of PM K-25 1:1

The solvent evaporation method resulted essential changes in the molecular state of NIF by **FT-IR**. Two strong bands disappeared from the original spectra at 1615 and 1428 cm^{-1} a new one developed at 1683 cm^{-1}. Fast evaporation of the solvent and the formation of an amorphous, highly dispersed, solid phase prevents the transfer of the proton, which resulted a higher energy state, higher equilibrium concentration and higher solubility.

The **XRPD peaks** of NIF in the PMs K-25 were similar to those for the pure drug, indicating that the crystallinity of NIF was not changed in these products. However, the crystalline structures of NIF in all the solid dispersions were different from that of the pure drug, as revealed by the differences in their XRPD patterns. These patterns were similar to those for the PVPs. The absence of diffraction peaks indicated the presence of NIF in amorphous form (Fig. 7).
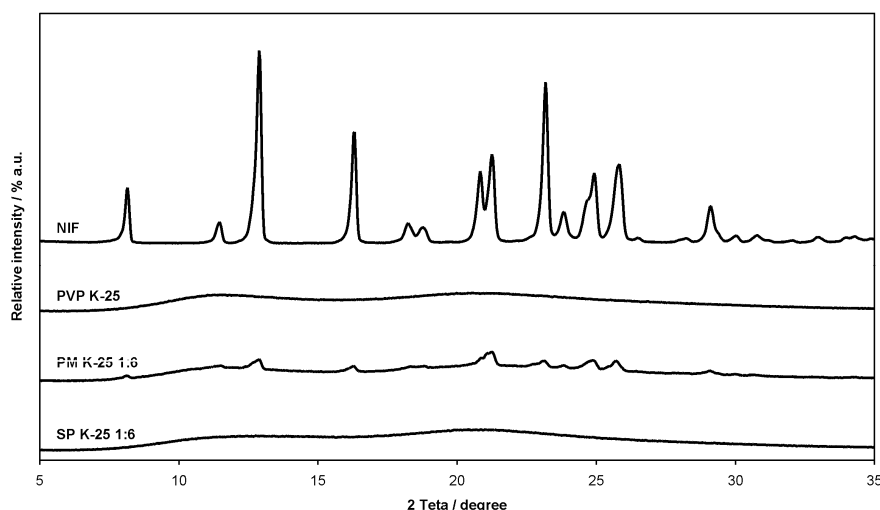
Fig. 7. XRPD patterns of NIF, PVP K-25, PM K-25 1:6 and SP K-25 1:6

6. SUMMARY

In consequence of the poor water-solubility of the pharmaceutical ingredient, NIF, my aim was to increase its solubility and dissolution rate by applying several methods. This work involved a preformulation study to introduce the technological possibilities of a generic formulation.

The research work can be summarized as follows:

1) The solubility-increasing effects of the available CD derivatives were determined under uniform conditions. It was found, that the solubility of NIF was always increased by the CDs, and especially for NIF with HP-β-CD to 2.5-fold.

2) Different preparative mole ratios (2:1, 1:1, 1:2 and 1:3) and three methods (PMs-physical mixtures, KPs-kneaded products and USs-ultrasonicated products) were applied to form complexes, and 15 m/m% PVP K-90 was used to prepare ternary systems (PMs+PVP and KPs+PVP) to improve the efficacy of complexation.

3) To observe the good effect of a water-soluble polymer, PVP, on the complexation, solid dispersions were prepared in various mass ratios (1:1, 1:2, 1:4, 1:5, 1:6 and 1:10), using different types of PVP and applying three methods (PMs, SPs-solvented products and SPDs-spray-dried products).

4) The wettability study indicated that the products had a hydrophilic character as compared with NIF. Significantly lower wetting angles were measured for all samples, the decrease ranging from 71º to 26º. There was a parallel result for the wettability relative to the saturation concentration in water. A significant difference was observed

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for the SPDs, where the concentration was 413 μg/ml compared with the pure NIF (26 μg/ml).

5) A concerns the morphology of the solid dispersions, determined via particle size analysis, the average lenght of the crystalline drug was changed during the solvent evaporation method, the size decreasing from 45 μm to 13 μm. These products have small particles, which is important in the formulation of solid dosage forms.

6) 38 different samples were examined as regards their dissolution with the rotating basket tester in SGM and SIM. The dissolution was better in SIM for all samples, except the binary kneaded products. The same dissolution phenomena were observed for the KPs, KPs+PVP, SPs and SPDs in SGM, where a 4-fold solubility increase was detected. In SIM, depending the preparation methods, 3.5 (KPs), 7.5 (KPs+PVP) and 14 (SPs and SPDs)-fold increases were demonstrated.

7) The intensity of the dissolution depended on the preparation method. The PMs and the USs always displayed prolonged dissolution profiles. The addition of PVP and the use of an organic solvent, such as ethanol, methanol or acetone containing amorphous material led to rapid dissolution. It was also typical that the saturation concentration was reached in 5–10 min for solid dispersions, while the samples containing CDs needed 15–20 min to reach the same state. The dissolution rate increase was 1.5–2.5-fold for binary and ternary systems with CD, and 5–51-fold for the solid dispersions.

8) According to the BCS, NIF has good permeability and very bad solubility, which is reflected by the n-octanol distribution, which showed the high n-octanol solubility and low water solubility of NIF. The products resulted in a 2–4-fold better diffusion as compared with the original NIF in SGM. NIF had a K_d value of 2.36 10^{-3} cm min^{-1}, while the K_d values for the samples were improved. The SD and SPD with a mass ratio of 1:1 displayed the highest K_d values.

9) The DSC curves demonstrated crystalline NIF for samples containing CD. When PVP was used, the melting point of the drug was not detected. During heating, the drug particle size was steadily reduced, showing its dissolution in the PVP melt. The NIF was completely dissolved in the melt of PVP at close to 157 ^{o}C, a temperature about 50 ^{o}C lower than the melting point of the pure drug. This finding can explain the absence of any sign of melting in the DSC thermograms of the PMs K-25.

10) The structural characterization, like the FT-IR spectra, did not show new bonds in the case of samples with CDs. Thus, no inclusion complexation was presumable. However, for the solid dispersion systems, where two strong bands disappeared from the original spectra, at 1615 and 1428 cm^{-1}, a new one developed at 1683 cm^{-1}.

11) The crystalline structures of NIF in all the solid dispersions were different from that of the pure drug, as revealed by the differences in their XRPD patterns. These patterns were similar to those for the PVPs. The absence of diffraction peaks indicated the presence of NIF in amorphous form. This is a higher energy state for the solid phase, resulting in a higher equilibrium concentration and a higher solubility.
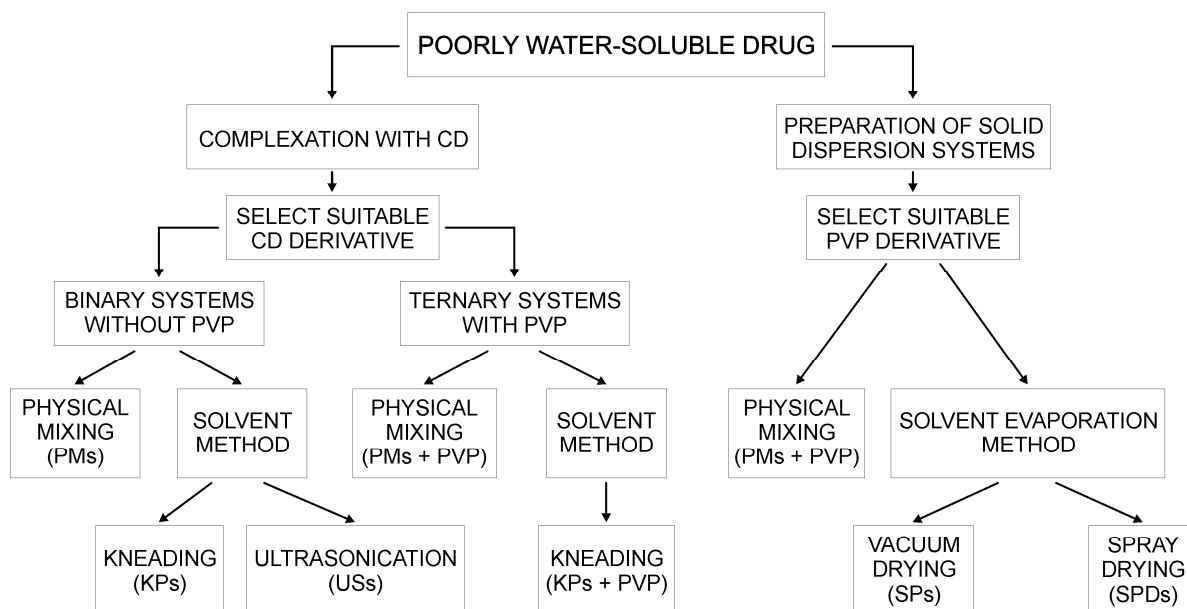

Fig. 8. Summarized technological protocol of the Thesis

To summarize the results, the goal of this study that the solid dispersion systems are more favourable than using CD to improve the solubility and dissolution rate of nifluminic acid. Using CD, I suggest the ultrasonicated binary and the kneaded ternary 1:3 products to prepare semisolid dosage forms. In these cases the permeability and wettability properties of the drug are very useful. Spray-drying, like the solvent evaporation method using 30 v/v% of ethanol, resulted in rapid drug release, it is suitable for solid dosage form formulation. After this substantial preformulation study, further biopharmaceutical investigations should be performed, like gastric toxicity, blood level concentration and oedema inhibiting effect of the products. Fig. 8 present the steps of the technological protocol in the case of nifluminic acid. These methods may help by the generic formulation of other poorly water-soluble pharmacons, so the applied drug quantity and the unwanted side-effects can therefore be decreased.

ANNEX

Publications

I. M. Kata, **R. Ambrus** and Z. Aigner: *Preparation and investigation of inclusion complexes containing nifluminic acid and cyclodextrins.* J. Incl. Phenom. **44**, 123–126 (2002) (**IF 2005: 1,02**)

II. **Ambrus R.**, Kata M., Erős I. és Aigner Z.: *Nifluminsav oldékonysági tulajdonságainak növelése ciklodextrin és polividon felhasználásával.* Acta Pharm. Hung. **75**, 31–36 (2005)

III. **Ambrus R.**, Kata M., Erős I. és Aigner Z.: *Vízoldékony polimer befolyása ciklodextrines zárványkomplex-képződésre.* Orvostudományi Értesítő **78** (2), 200–205 (2005)

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