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Dropping method as a new possibility in preparation of solid dispersions

Summary of PhD thesis

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Szeged
Hungary
2007

1. Introduction

One of the challenging tasks in manufacturing process is to improve the bioavailability of poorly water-soluble drugs. In recent years, an increasing number of active agents posses low aqueous solubility. As a result, oral delivery of poorly water-soluble drugs often results in low bioavailability. Various methods have been introduced to enhance the bioavailability of the poorly water-soluble drugs, which can be summarized in physical and chemical modifications.

Among these methods, preparation of *solid dispersion* has become one of the most active areas of research in the pharmaceutical field to improve the bioavailability of poorly water-soluble drugs. This method involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixture, which resulted in solubility enhancement.

Numerous papers on various aspects of solid dispersion have been published and despite early promising results in laboratory scale, the commercial application of solid dispersion in dosage form design has been very limited. Problems limiting the commercial application of solid dispersion involve its method of preparation, reproducibility, its formulation into dosage forms, the scale up manufacturing processes, and the physical and chemical stability of drug and vehicle.

Dropping method as a new possibility in preparation of solid dispersion helps to overcome some of the manufacturing difficulties. Dropping method facilitates the crystallization of different chemicals, is a new procedure for producing *round particles* from melted solid dispersions. Round particles produced by dropping method can be used directly as ready dosage form or it can be filled into capsules. Round particles can be processed further for coating if desired. This is a cost-effective method, which simplifies the production process by avoiding the pulverization, sifting, and compressibility difficulties encountered with the other melt methods. Dropping method a green technology, which avoids the use of harmful materials to our environment.

2. Aims

The aim of this PhD work was to produce solid dispersion of poorly water-soluble drugs with the use of new pharmaceutical technology methods, which simplifies the process of production and scale up. For this purpose two sets of experiments were carried out using Levodopa and Meloxicam as poorly water-soluble drugs. Developing the new technology was with special regard to fast drug release from the product.

The following objectives were set:

- The overview of the literature related to the subject;
- Performing two sets of experiments with two different compounds (Levodopa and Meloxicam as poorly water-soluble drugs) to evaluate the new technology;
- Investigation of the carriers, applicability and reproducibility of the new technology.

At first set of experiments Levedopa were used to carry out the preformulation studies to investigate the applicability of the new technology. At second set Meloxicam were formulated by dropping method and wider investigations were applied for better understanding of the new technology.

3. Materials and methods

Materials

- Levodopa (Dihydroxy-fenylanaline, melting range: 276-286 °C) one of the most effective active agents for the management of Parkinson's disease were used as poorly water-soluble drug in preformulation studies.
- Meloxicam (ME) (melting range: 258-261 °C) is an effective NSAID with poorly water-soluble characteristic. All other reagents and solvents were of analytical grade.
- Polyethylene glycol (PEG) 4000 (melting range: 50-58 °C) was used as water-soluble carrier for preparation of the solid dispersions.

The ratio of the drug-PEG 4000 mixtures at both sets was 1:3 respectively.

Methods

Conventional method

For the preparation of a Levodopa-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and melted at 58 °C (± 1 °C) and a measured amount of Levodopa was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-μm mesh. 60 mg of Levodopa-PEG 4000 powder (containing 15 mg of Levodopa and 45 mg of PEG 4000) was filled into a hard gelatin capsule (size no 2) for further investigations.

Direct capsule filling method

For the preparation of the Levodopa-PEG 4000 solid dispersion by direct capsule filling method, PEG 4000 was weighed and melted in a double-layered beaker at 58 °C (± 1 °C) and a measured amount of Levodopa was added and stirred. The measured amounts of Levodopa and PEG 4000 corresponded to a drug - carrier ratio of 1:3. 60 mg of drug-carrier mixture was filled directly into a hard gelatin capsule (size no 2) for further investigations.

Preparation of physical mixture

For the preparation of a ME-PEG 4000 physical mixture, ME and PEG 4000 were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400-μm mesh. 60 mg of ME - PEG 4000 powder mixture (containing 15 mg of ME and 45 mg of PEG 4000) was filled into a hard gelatin capsule (size no 2) for further investigations.

Tablet-making

ME - PEG 4000 tablets were prepared with a Korsch EKO eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single, flat punches 10 mm in diameter, furnished with strain gauges. The physical mixture of ME - PEG 4000 was compressed at a pressure of 10 ± 1 kN at an air temperature of 24 °C and an air relative humidity of 45%. The crushing strength of the tablets was investigated with a Heberlein apparatus (Flisa, Le Locle, Switzerland). The geometrical parameters were measured with a screw micrometer (Mitutoyo, Japan). The weight of the tablets was calibrated to 60 mg. Each tablet contained 15 mg of ME and 45 mg of PEG 4000.

Dropping method

For the preparation of the Levodopa-PEG 4000 solid dispersion by dropping method, PEG 4000 was weighed and melted in a double-layered beaker at 58 °C (± 1 °C) and a measured amount of Levodopa was added and stirred. The measured amounts of Levodopa and PEG 4000 corresponded to a drug-carrier ratio of 1:3 (each solid drop contained 5 mg of Levodopa and 15 mg of PEG 4000). The melted drug-carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug-carrier mixture was dropped onto a stainless steel plate, where it solidified into round particles. The surface free energy of the plate was 29.73 mN/m. The temperature of the stainless steel plate was 20 °C (± 1 °C). Three round particles (60

mg) were placed into hard gelatin capsules (size no. 2) for further investigations. For this purpose an special equipment developed by Bülau and Ulrich were used (Fig. 1.)

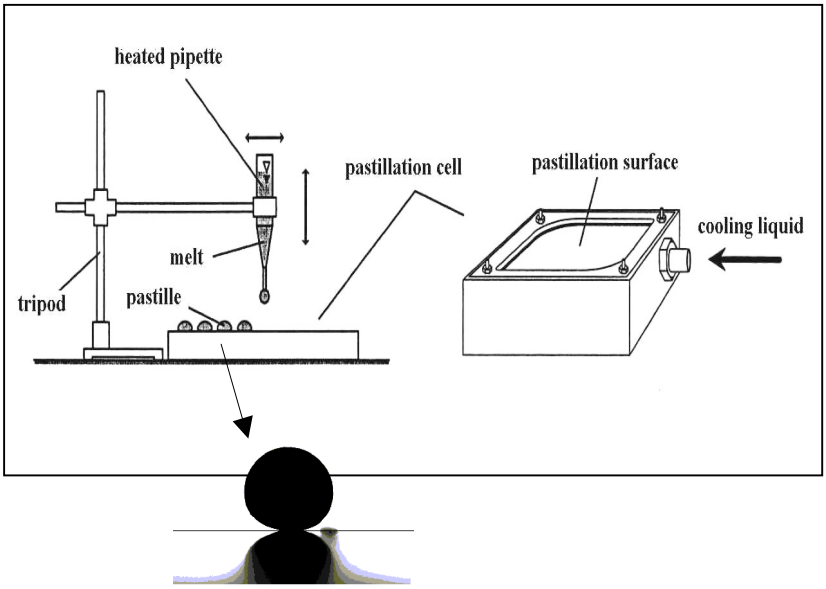

Fig. 1. Equipment used for dropping method with solid drops

For the preparation of the ME - PEG 4000 solid dispersion by the dropping method, PEG 4000 was weighed and melted in a double-layered beaker at 58 °C (± 1 °C) and a measured amount of ME was added and stirred. The measured amounts of ME and PEG 4000 corresponded to a drug - carrier ratio of 1:3 (each solid drop contained 5 mg of ME and 15 mg of PEG 4000). The melted drug - carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant. The melted drug - carrier mixture was dropped onto a stainless steel plate, where it solidified into round particles. The temperature of the stainless steel plate was 20 °C (± 1 °C). Three round particles (60 mg) were placed into hard gelatin capsules (size no. 2) for further investigations.

In vitro dissolution studies

Samples of conventional, direct capsule filling and dropping method containing Levodopa were prepared for dissolution studies. Samples were filled into hard gelatin capsules (size no. 2). Each capsule contained 15 mg of Levodopa and 45 mg of PEG 4000. Dissolution tests were performed with a Pharmatest (Hainburg, Germany) dissolution tester, set with a paddle speed of 100 rpm. Artificial enteric juice (900 ml) with a pH of 7.5 (± 0.1) at 37 °C (± 0.5 °C) was used. Samples were withdrawn at 5, 10,

20, 30 and 60 minutes, and were assayed spectrophotometrically at 280 nm (Helios α, Spectronic Unicam, Cambridge, UK) after filtering.

Dissolution studies for samples containing ME were carried out as follow: Samples of tablets, physical mixture, pure ME and round particles were prepared for dissolution studies. The physical mixture, round particles and pure ME as reference sample were filled into hard gelatin capsules (size no. 2). Each capsule contained 15 mg of ME and 45 mg of PEG 4000. Dissolution tests were performed with a Pharmatest (Hainburg, Germany) dissolution tester, set with a paddle speed of 100 rpm. Artificial enteric juice (900 ml) with a pH of 7.5 (± 0.1) at 37 °C (± 0.5 °C) was used. Samples were withdrawn at 5, 10, 20, 30, 60 and 90 min, and were assayed spectrophotometrically at 361 nm (Helios α, Spectronic Unicam, Cambridge, UK) after filtering.

Differential scanning calorimetry (DSC)

Thermal analysis was carried out with a DSC instrument (Mettler-Toledo GmbH, Switzerland). Sample was weighed into a non-hermetically sealed aluminum pan. The samples were heated from 25 to 400 °C at a heating rate of 5 °C/min for Levodopa. In case of ME the samples were heated from 25 to 300 °C at a heating rate of 5 °C/min and 30 °C/min. The instrument was calibrated by using indium.

X-ray powder diffractometry (XRPD)

XRPD was performed with a Philips X-ray diffractometer (PW 1050/70 PW 1710). The measurement conditions were: radiation source: CuKα, scan speed (2θ/s): 0.035, step size (2θ/s): 0.035, time per step: 1.0.s.

Investigation of particle size

The particle size distribution of the ME was measured by laser diffraction (Malvern Mastersizer 2000, Malvern Ltd., Worcestershire, UK). For the measurements, the samples were dispersed in air and deagglomerated at an air pressure of 1 bar. The particle size was determined in the range 0.02-2000 μm and the measurements were repeated three times. The particle size of the product obtained with the dropping method (S3) was determined with a screw micrometer (Mitutoyo, Japan).

Kinetic calculation by Langenbucher

The dissolution profiles of samples and pure ME can be described by modified Langenbucher model (Langenbucher, 1976).

$$\sqrt[3]{1-\frac{m_t}{m_0}} = \ln t$$

where m_0, the mass of the drug at time $t=0$ and m_t, at time t. The linear transformation resulted in the rate constant (k value) and the intercept value (n).

Chemometric method

Fiala developed a procedure, correlation analysis, for the XRPD analysis of mixtures of components. Nassab et al. introduced a multivariate curve resolution method for the same purpose, but without reference to the Joint Committee on Powder Diffraction Standards (JCPDS). The chemometric method of multivariate curve resolution with alternative least squares (MCR-ALS) can break the data matrix down into profiles (composition profiles and pure diffractogram profiles) with the use of certain constraints. Unfortunately, this decomposition is very often not unique because of the rotational and intensity (scaling) ambiguities. The rotational ambiguities can be moderated or even eliminated if convenient constraints can be used.

The self - modeling curve resolution (SMCR) method, one of the oldest chemometric procedures, was introduced for two-component systems by Lawton and Sylvestre to deconvolve raw spectroscopic data into the product of two physically interpretable profile matrices provided that both concentrations and absorbances are non-negative, accepting both as minimal constraints. Unfortunately, the solution is not unique: the method can give feasible regions only for the pure component profiles without further restrictions. Borgen et al. generalized the LS method for three-component systems with the same minimal constraints. Rajkó et al. recently revisited Borgen's method, gave a clearer interpretation and used computational geometry tools to find inner and outer polygons. We will introduce the SMCR method to evaluate XRPD data in for Meloxicam investigations.

Determination of surface free energy

The product shape is influenced by the surface free energy of the cooling surface in the melt solidification technology. The surface free energy can be calculated from the contact angles between the surface and test liquids and contact angles can be determined with *Drop Shape Analyzers*. Figure 2. Shows contact angles of water on different surfaces.

water on glass water on teflon water on steel

Fig. 2. Contact angles of water on different surfaces

4. Results and discussion

Melt solidification technology requires a surface with moderate surface free energy. In the case of high surface free energy the melt drop may become deformed during solidification, and on a surface with low surface free energy the drop may flow before solidification as a round particle. Consequently, our choice fell on steel surface to produce spherical particles with special hot melt technology.

Results of preformulation studies using Levodopa

Preformulation studies were carried out to determine the most suitable ratio of the Levodopa-PEG 4000 mixture. The sample involving a drug-carrier ratio of 1:3 with PEG 4000 as carrier exhibited the best drug release properties.

Solid dispersions of Levodopa-PEG 4000 were prepared by conventional method (series 3), direct capsule filling method (series 2) and dropping method (series 1) to compare their dissolution rates. The results of the dissolution tests show that the solid dispersions made by the dropping method have better drug release properties than those produced by the other to methods, particularly during the first 20 minutes (Fig. 3). Another aspect of preformulation studies was to investigate the applicability of the dropping method to produce spherical particles.

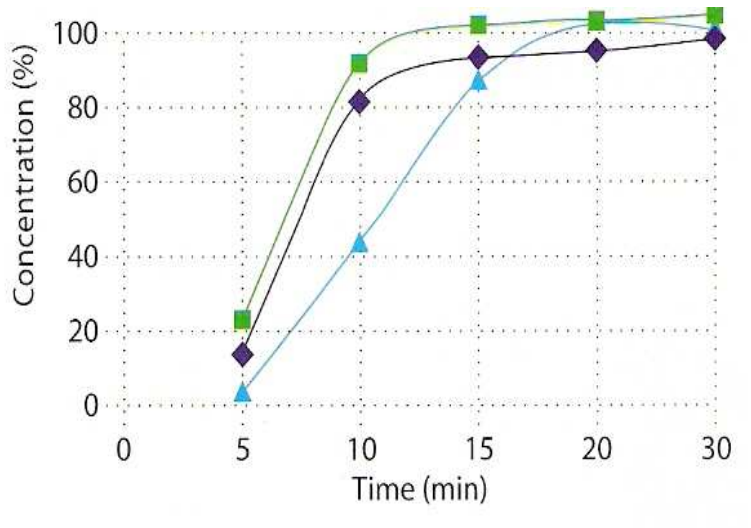

Fig. 3. Comparison of dissolution rates of solid dispersions produced by three methods. ■ Series 1: samples made by dropping method. ♦ Series 2: samples made by direct capsule filling method. ▲ Series 3: samples made by conventional method

Result of the DSC investigation of pure levodopa shows the decomposition prior to melting at 281 °C. In case of the samples, which contain PEG 4000 the decomposition stage is shifted to 370 °C. On the other hand, in case of samples where Levodopa was added to the melted PEG 4000 lower energy is required to initialize the melting process of the levodopa. This means that part of the levodopa crystals were dissolved or converted to a new crystal in presence of melted PEG 4000, which results in better dissolution properties.

Better dissolution rate of round particles than samples made by direct capsule filling method is also influenced by its bigger surface area and lack of the plaque, which may occur in case of direct capsule filling method.

Structural changes of Levodopa crystals in different samples were investigated by XRPD. XRPD investigation shows that Levodopa crystals were changed when blended with PEG 4000. Some of the peaks appeared in the diffractogram of pure levodopa disappeared in diffractograms of the samples where levodopa was blended with PEG 4000. Furthermore, samples prepared by dropping method show fewer peaks than the samples prepared by physical mixture. Results of XRPD investigation show that the crystallinity of the Levodopa decreases by blending in melted PEG 4000. This changes of the crystals promotes the solubility of the Levodopa.

Results and discussions for Meloxicam

The particle size distribution of ME is important as concerns the wettability properties and dissolution: the relatively small particle size of ME promotes its dissolution rate when it is blended with PEG 4000. For the development of the product, micronized ME was chosen because of its ideal particle size and specific surface. The particle size distribution of ME at D 90% was 5.97 µm (STDEV ± 0.31) and at D 10% was 0.73 µm (STDEV ± 0.01).

Preformulation studies were carried out to determine the most suitable ratio of the drug - carrier mixture. The sample involving a drug - carrier ratio of 1:3 with PEG 4000 as carrier exhibited the best drug release properties.

Tablets (as the most frequently used dosage form), physical mixtures and round particles (solid drops) were compared with the pure drug in order to determine and compare the drug - release properties.

The rates of dissolution of the above - mentioned three samples and pure drug were measured and are shown in Figure 4, which demonstrates that all three samples dissolved faster than the pure drug and there was a significant increase in the rate of dissolution of the sample made by the dropping method (S3).

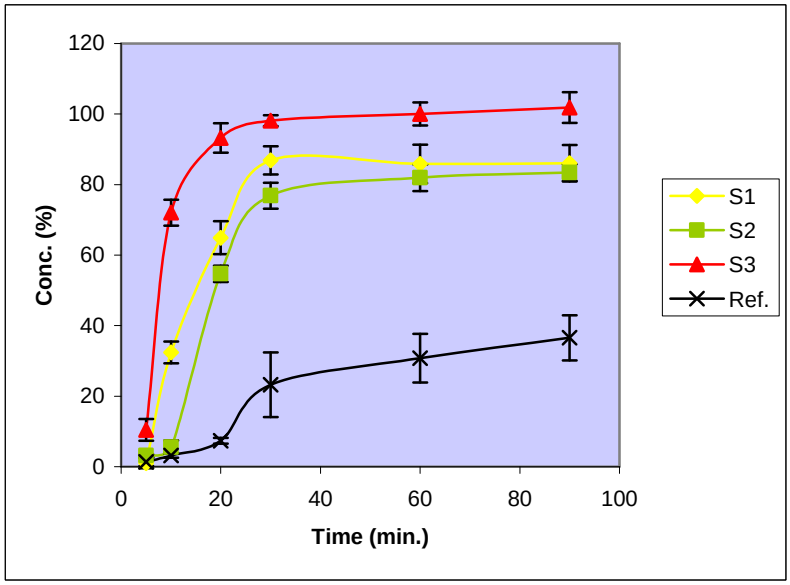

Fig. 4. Rates of dissolution of different samples. Ref.: pure ME, S1: physical mixture, S2: tablet, S3: round particles developed by dropping method

Further examinations (DSC, XRPD and chemometric analyses) were carried out to find out why samples made by the dropping method had better dissolution properties than the other samples.

The DSC method was used to determine the physical-chemical properties of ME and the binary systems (physical mixture and round particles). The thermogram of ME exhibited a sharp endothermic peak at 260 °C, corresponding to the melting point of ME. In the sample (S1 and S3) where PEG 4000 was present, the peak was about 62 °C for PEG 4000 and 219 °C for ME due to the partly dissolving of ME in the melted PEG 4000 (Fig. 5). This phenomenon appeared in the dropping method too, where ME was added to melted PEG 4000. In the cases of the tablets and physical mixture, no heat was applied, so there was no possibility for ME to dissolve in PEG 4000. This might be one of the reasons why the samples formulated by the dropping method exhibited better dissolution than the tablets and physical mixtures.

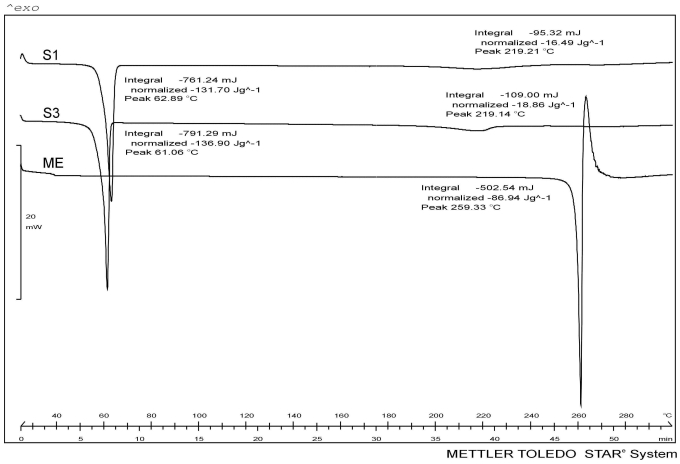

Fig. 5. DSC curves of pure ME, physical mixture (S1) and round particles made by the dropping method (S3) at heating rate of 5 °C/min

X-ray powder diffraction was used to investigate the starting materials ME, PEG 4000a (untreated, commercial) and PEG 4000b (melted and solidified) and also the sample made by the dropping method (S3) and the physical mixture (S1) (Fig. 6). Visual inspection did not reveal any significant difference in crystal structure, i.e. the diffractograms of the physical mixture and the particles made by the dropping method seemed to be very similar. The diffractograms of S1 and S3 displayed the characteristic values of the starting materials. It is clear that, in the case of S3, the crystals of ME that dissolved in the melted PEG 4000 recrystallized during cooling. The round particles contained the recrystallized ME in suspended form. Consequently, the DSC and XRPD studies demonstrated the stable crystalline form of ME in S3 and the absence of any well defined ME - PEG 4000 interaction.

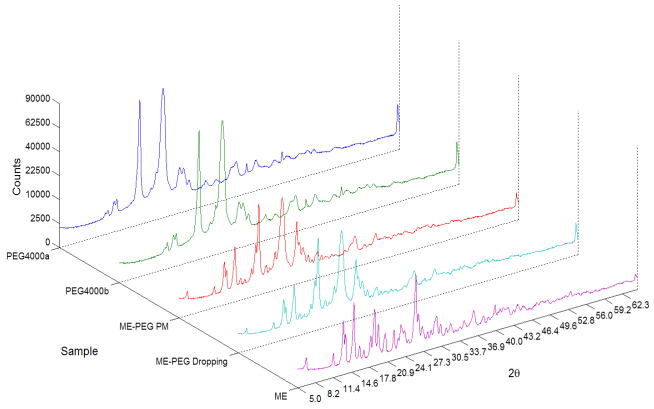

Fig. 6. X-ray powder diffraction. Starting material: ME (pure), PEG 4000a (untreated, commercial) and PEG 4000b (melted and solidified). Samples: S1 - physical mixture (ME - PEG PM), S3 - round particle (ME - PEG dropping)

The question arose of whether the fast and quantitative dissolution of ME from S3 can be explained only in terms of the melt technology and/or the homogeneous distribution of ME in the solid dispersion. To investigate this, a chemometric method, SMCR, was used. Based on the three components given by the SMCR method, the bands of the diffractograms indicate PEG 4000, ME and a new (mixed) crystal form. The estimated bands for the compositions of the samples were first calculated via the unconstrained SMCR method. Constraints can be applied to make bands as narrow as possible. The ME content in the PEG 4000 sample is zero or near to zero, the PEG 4000 content in the ME sample is zero, and the new mixed crystal form content in the ME and PEG 4000 samples is zero or as little as possible. It can be concluded that the content of the new mixed crystal form is smaller in the physical mixture, while both the PEG 4000 and ME contents are decreased in the round particles made by the dropping method, and additionally the content of the new crystal form is increased. The explanation is as follow; The SMCR calculation indicated a small amount of the new mixed crystal form in the physical mixture (S1). This suggests rearrangement of ME and PEG 4000 in the binary system because of the mechanical effects (mixing, friction and heat). The melt technology naturally results in a greater change in the structure of the binary system, with the appearance of the new mixed crystal form.

This is connected with the partial dissolution of the ME in the melted PEG 4000 and the fast solidification of the drops. Some of the dissolved ME return to the original state after solidification, while the remainder of the ME, in the form of molecule-clusters, is incorporated in the macromolecules of PEG 4000. This interaction between ME and

PEG 4000 does not give a different appearance to the X-ray diffractogram because of the overlapping of the characteristic values, but the chemometric method demonstrated the presence of the new mixed crystal form, which resulted in fast and quantitative dissolution from the solid dispersion of S3.

5. Summary

The aim of my PhD work was to adopt a new technology to increase the bioavailability of the poorly water-soluble drugs and to prepare a solid dosage form using dropping method which is a special hot melt technology. By this method solid dosage form can be produced by a single step process, which, simplifies the manufacturing process. The role of the applied technology to increase the drug release properties of the poorly water-soluble drugs was in focus as well as the carriers.

For this purpose Levodopa and Meloxicam as poorly water-soluble compounds were selected and two sets of investigations were applied separately with same conditions.

The production of the spherical particles by dropping method was in Germany, at the Institute of Process Engineering of Martin Luther University, Halle-Wittenberg.

Levodopa as a poorly water-soluble drug was used at first set of experiments for preformulation studies. Different carriers and their combination with different drug-carrier ratio were used to increase the dissolution rate of the levodopa. Best result were achieved when levodopa were added to PEG 4000 with 1:3 drug-carrier ratio and this was the most suitable carrier to produce spherical particles by dropping method. Results of the preformulation studies show that samples prepared by dropping method had better dissolution properties than the others. On the other hand the process of production were simplified and the products were prepared by a single (dropping) step without any need for further processing.

Promising results from preformulation studies encouraged us to apply the dropping method with another poorly water-soluble drug and to apply more investigations for better understanding of this new technology. For this purpose Meloxicam a poorly water-soluble drug were used for second set of experiments. Samples of Meloxicam-PEG 4000 solid dispersions were prepared according to protocol developed by preformulation studies of Levodopa-PEG 4000 (Fig. 7).

Protocol of dropping method

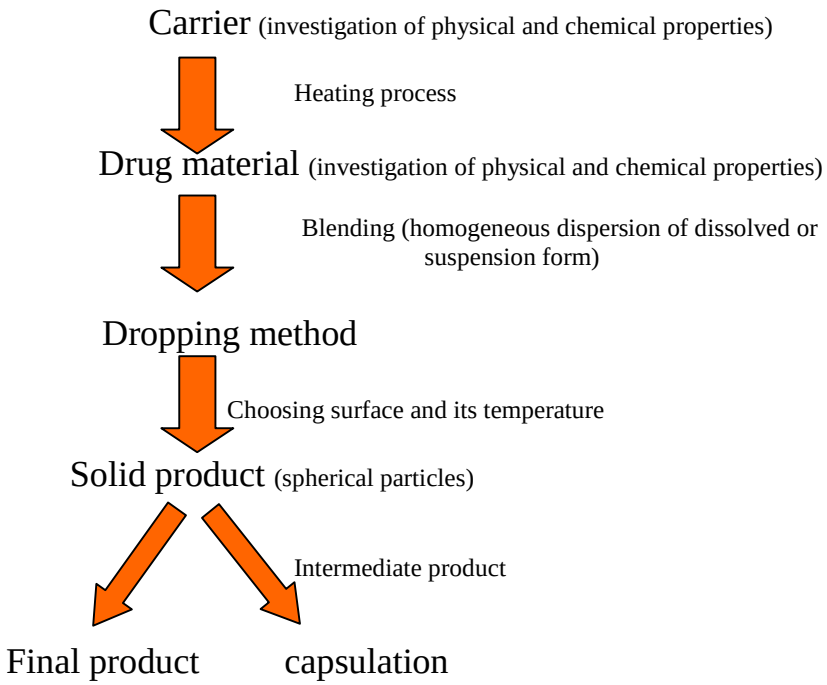

Fig. 7. Formulation of solid dispersion by dropping method

Wider investigations and tests were applied on Meloxicam-PEG 4000 samples after achieving the similar good results as preformulation studies. Physical and chemical tests were applied to investigate the behavior of the Meloxicam and PEG 4000 crystals. Such investigations (DSC, XRPD, Chemometric, Dissolution test) showed that the better solubility of the samples prepared by dropping method (spherical particles) is the result of the applied technology. The reason for increased solubility characteristic of samples prepared by dropping method can be explained with partial dissolution of the poorly water-soluble drug in water-soluble carrier (solid dispersion) and formation of the new drug-carrier crystals (solid solution), which, investigated by chemometric, analyzes. It can concluded that:

- Dropping method is an applicable method for preparation of solid dispersions.
- Dropping method can increase the bioavailability of the poorly water-soluble drugs.
- The process of production can be simplified.

Acknowledgement

I would like to thank
Professor Dr. Piroska Szabó-Révész
Head of Department of Pharmaceutical Technology for providing the possibility to complete my work under her advice and her valuable assistance in the practical work and during my complete research.

My sincere thanks go to
Professor Dr. István Erős
For his help in my reaserch.

I express my grateful thanks to
Professor Dr. Joachim Ulrich
Head of Department of process Engineering, Martin-luther University, Halle-Wittenberg, for providing the possibility to do scientific research in his department.

I express my grateful thanks to my co-authors:
Dr. Rajkó Róbert, Parya Reisi Nassab, Dr. Magdolna Hasznos-Nezdei
For their co-operation.

I thank all members of the department for their help.

I express my grateful thanks to my family for their support, encouragement and understanding attitude during these years.

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