Doctoral dissertation

DROPPING METHOD AS A NEW POSSIBILITY IN PREPARATION OF SOLID DISPERSIONS

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Publications

I. **Bashiri-Shahroodi, A**., P. Szabó-Révész, I. Erős:
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II. Hasznos-Nezdei, M., J. Kovács, S. Kováts, **A. Bashiri-Shahroodi**, P. Szabó-Révész
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III. Nassab, P.R., Zs. Tüske, P. Kása, **A. Bashiri-Shahroodi**, P. Szabó-Révész
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IV. **Bashiri-Shahroodi, A.,** R. Rajkó, P. R. Nassab, P. Szabó-Révész
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Abstracts

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IV. Reisi Nassab, P., P. Szabó-Révész, **A. Bashiri Shahroodi**, I. Erős:
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Contents

1. Introduction

Under the present health care economic climate, the goal of any drug development program in the pharmaceutical industry is to rapidly progress a new chemical entity from the discovery stage to clinical testing to determine whether it is safe and clinically effective. A compound may proves promising in early clinical testing, but the scale up of complex manufacturing processes for the development of marketable dosage forms causes many difficulties.

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. Literature

2.1 Solid dispersion in general

The bioavailability of a poorly water-soluble drug is often limited by its dissolution rate, which is in turn controlled by the surface area available for dissolution. The effect of particle size of a drug on its dissolution rate and its biologic activity is well known [1]. Atkinson and associates [2] reported that the therapeutic dose of griseofulvin was reduced by half after micronization. A more constant and reliable blood level profile was also obtained.

The conventional methods for reducing particle size include trituration and grinding, ball milling, fluid energy micronization, and controlled precipitation [3]. Alternately, micronized particle formation may be accomplished in situ by one of the two following techniques: (1) liquid solutions using nonaqueous solvents could be administered from which, upon dilution with gastric fluids, the dissolved drug may precipitate in very fine particles [4]; or (2) water-soluble salts of poorly soluble drugs could be administered from which the parent drug may precipitate in ultra fine form in gastrointestinal fluids. Although reduction in particle size can be easily and directly accomplished by the first four methods, the anticipated increase in availability may not be achieved. This has been attributed to aggregation and agglomeration [5] or air adsorption [6], which may result in poor powder wettability that reduces the effective surface area.

Co-precipitates and melts are solid dispersions that provide a means of reducing particle size to the molecular level. The concept of using solid dispersions to improve bioavailability of poorly water-soluble drugs was first introduced by Sekiguchi and Obi [7] in 1961. They demonstrated that the eutectic mixture of sulfathiazole and the physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration than sulfathiazole alone.

Chiou and Riegelman [3] defined the term *solid dispersion* as ‘‘a dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method’’. Dispersions obtained through the fusion process are often called melts, and those obtained by the solvent method are frequently referred to as *co-precipitates* or *co-evaporates*, for example, sulfathiazole-povidone (PVP) [8] and reserpine-PVP [9].

2.2 Methods of Preparation

The two basic procedures used to prepare solid dispersions are the fusion and co-solvent techniques. Modifications of these methods and combination of them have also been used [3].

2.2.1 Melting or Fusion Method

This method was first reported by Sekiguchi and Obi [7]. A physical mixture of an active agent and a water-soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath under rigorous stirring, pulverized, and then sieved. Rapid congealing is desirable because it results in super saturation of drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. The solidification process can be achieved on stainless steel plates attached to a cooling system to favor rapid heat loss [10-14]. Spray congealing from a modified spray drier onto a cold metal surface has also been used [15,16]. Products from this process can be obtained in pellet form without the necessity of a grinding step that may alter crystalline modification.

Two advantages of the melt method are its simplicity and its economy, as no solvents are involved. However, the method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporates at high temperatures. Succinic acid, for example, used as a carrier for griseofulvin [13] is quite volatile and partially decomposes by dehydration near its melting point. Such problems can be avoided by melting in a sealed container, under vacuum or under an inert gas such as nitrogen [17]. By proper

selection of carrier system and composition, the melting point of a binary system can be much lower than the melting point of either of the components.

Other disadvantages of this method may include the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system.

2.2.2 Solvent Evaporation Method

Tachibana and Nakamura [18] first used this method to prepare a solid dispersion of carotene in PVP by using chloroform as a co-solvent. The solvent is usually removed by evaporation under reduced pressure at varying temperatures [10,19,20]. The choice of solvent and its removal rate are critical to the quality of the dispersion. A mixed solvent may be used [20]. Some examples of solid dispersions prepared by this method include: griseofulvin-PVP [21], sulfathiazole-PVP [8], reserpine-PVP [9], and reserpine-deoxycholic acid [19].

The freeze-drying process has been used to prepare dispersions of ketoprofen [22] and dicumarol [23] in PVP from their ammoniacal solutions. Similarly, the spray-drying process has been used to prepare dispersions of acetohexamide in PVP [24].

The major advantage of the solvent method is that thermal decomposition of drugs and carriers associated with the fusion method can be avoided. The disadvantages include:

- higher cost of preparation,
- use of large quantities of solvent and the difficulty in complete removal of solvent,
- possible adverse effect of residual solvent,
- selection of common volatile solvent,
- difficulty of reproducing crystal forms,
- inability to attain a super saturation of the solute in the solid system unless the system goes through a highly viscous phase,
- ecological and subsequent economic problems associated with the use of organic solvents.

2.2.3 Melt Extrusion

This technique, widely used in the plastic industry, has received attention in the pharmaceutical field as well. During the process, binder, excipients and active agents are fed into the heated barrel, and extruded through the die attached at the end of the barrel. The molten polymer rapidly solidifies when the extrudate exits the machine through the die. Extrudates then processed to form powders that are transformed into conventional dosage forms, or cut into small lengths to form pellets. By controlling the shape of the die, the final product may take the form of a film, pipe, granule or cylinder [25].

2.2.4 Direct Capsule Filling

In 1978, Francois and Jones [26] further developed the solid dispersion method by directly filling hard gelatin capsules with semisolids materials as a melt, which solidified at room temperature. Chatman [27] reported the possibility of preparing PEG-based solid dispersions by filling drug-PEG melts into hard gelatin capsules. Serjuddin et al. [28] demonstrated that PEG itself might not be a suitable carrier for the solid dispersion of poorly water-soluble drugs intended for direct filling into hard gelatin capsules. At room temperature, solid plugs were formed inside the capsules where the dissolution of the drug from PEG-based solid dispersions was incomplete. The water-soluble carrier dissolved more rapidly than the drug, and drug-rich layers were formed over the surfaces of the dissolving plugs, preventing further dissolution of the drug from solid dispersions. Studies report that complete dissolution of the drug from solid dispersions can be achieved using surface active or self-emulsifying carriers, but only a small number of such carriers are currently available for oral use. Some of the manufacturing problems mentioned earlier may be encountered in the direct capsule filling method.

2.2.5 Dropping Method as new method

The dropping method, developed by Bülau and Ulrich [29] to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. For this purpose an special equipment developed by Bülau and Ulrich were used (Fig. 1.) [29].

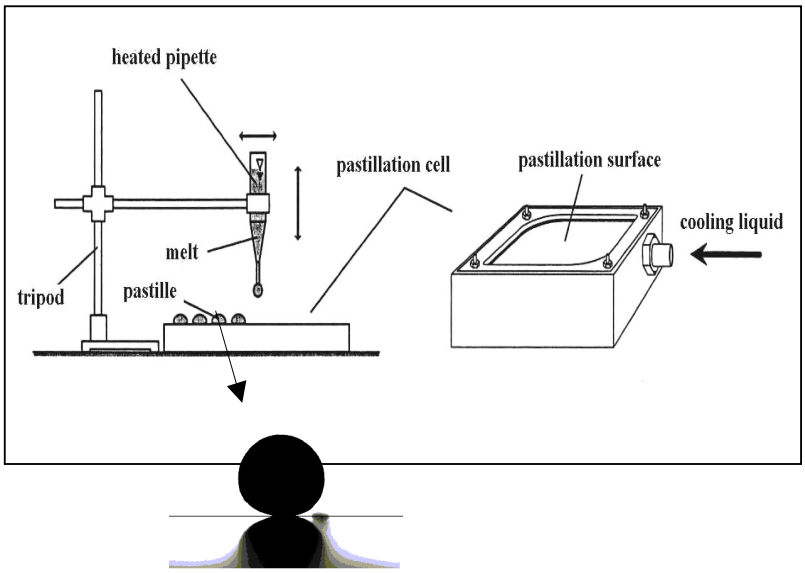

Fig. 1. Equipment used for dropping method with solid drops

Laboratory-scale preparation- Solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a cooling plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods, and there is no plug formation, mentioned in direct capsule filling method. The disadvantage is that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge.

2.3 Classification of Solid Dispersions

On the basis of their major fast-release mechanism, Chiou and Riegelman [3] classified solid dispersions into the following six representative types:

- Simple eutectic mixtures
- Solid solutions
- Glass solutions and glass suspensions
- Amorphous precipitations in a crystalline carrier
- Compound or complex formation
- Combinations of the previous five types

Many techniques have been used to characterize the physical nature of solid dispersions. These include thermal analysis (e.g., cooling-curve, thaw-melt, thermomicroscopy, and DTA methods), x-ray diffraction, microscopic, spectroscopic, dissolution rate, and thermodynamic methods. Usually, a combination of two or more methods is required to obtain a complete picture of the solid dispersion system.

2.3.1 Simple Eutectic Mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus, the x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components. A phase diagram of a two-component system is shown in Fig. 2. Examples of this type include phenacetine-phenobarbital [30], griseofulvin-succinic acid [31], and the dispersions of griseofulvin and tolbutamide in polyethylene glycol (PEG) 2000 [32].

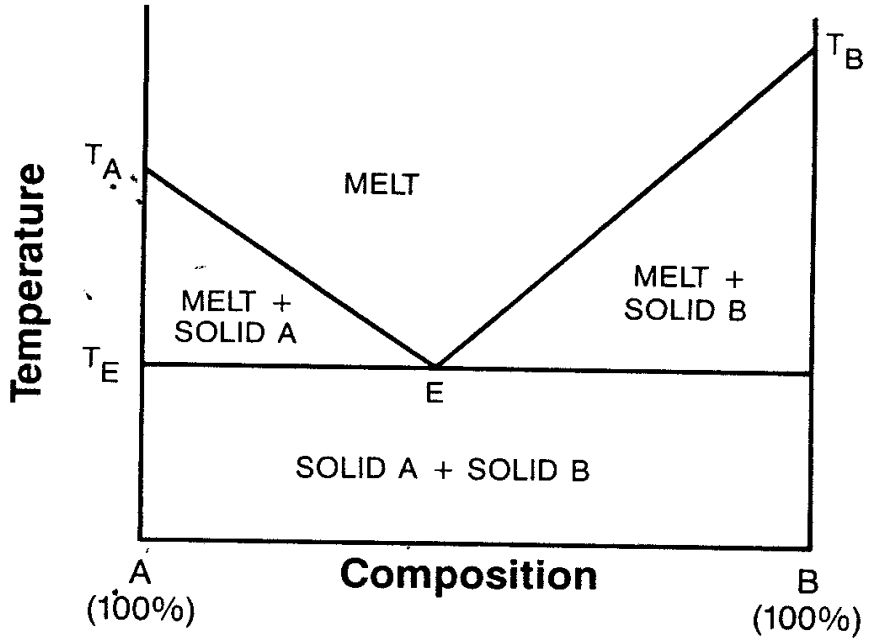

Fig. 2. Simple binary-phase diagram with eutectic formation. T_A is melting point of pure *A*; T_B is melting point of pure *B*; and *E* is eutectic point

2.3.2 Solid Solutions

In a solid solution the two components crystallize together in a homogeneous one-phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extend of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions. Typical phase diagram of continuous and discontinuous solid solutions are shown in Figs. 3 and 4, respectively. Discontinuous solutions exist at extremes of composition. In general, some solid-state solubility can be expected for all two-components systems.

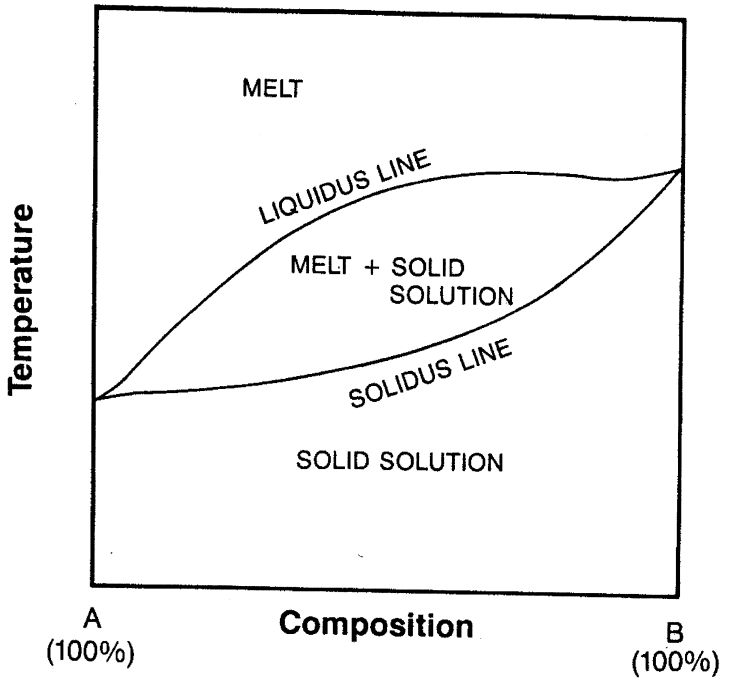

Fig. 3. A phase diagram of continuous solid solution for a binary system *A* and *B*

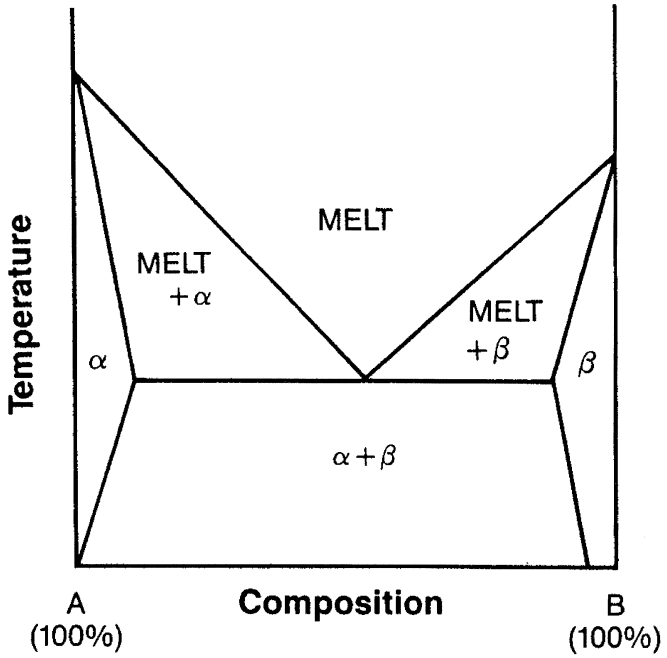

Fig. 4. A typical phase diagram of a discontinuous solid solution for a binary system A and B; α and β are regions of solid solution formation

According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional or interstitial. In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice (Fig. 5.). The molecular size of the two components should not differ by more than 15% [33]. This class is represented by solid solutions of *p*-dibromobenzene-*p*-chlorobromobenzene [34], anthracene-acenaphthene [35], and ammonium and potassium thiocyanate [36].

An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space (Fig. 5.) in the solvent (host) lattice. For this to occur, the solute molecule diameter should be less than 0.59 that of solvent molecule [37]; therefore the volume of the solute molecule should be less than 20% of the solvent molecule. Owing to their large molecular size, polymers favor the formation of interstitial solid solutions. Examples of this type include solid solutions of digitoxin, methyltestosterone, prednisolone acetate, and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit a fast rate of dissolution [3,10].

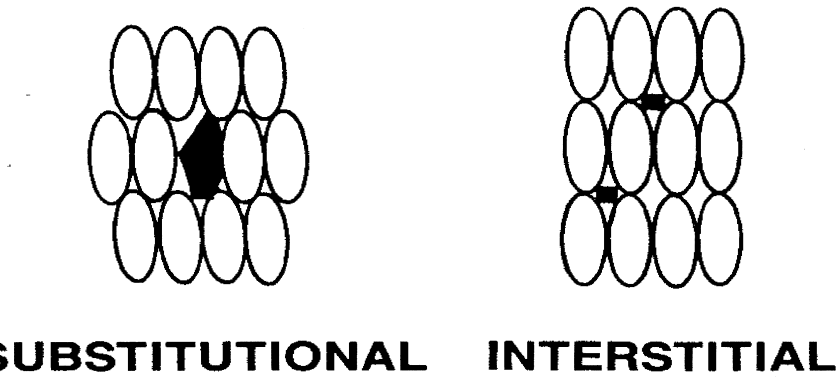

Fig. 5. Schematic representation of substitutional and interstitial solid solutions. Dark symbols represent solute atoms or molecules; open symbols indicate solvent atoms or molecules

2.3.3 Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting

points; instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Figure 6 shows the volume changes associated with glass formation when a melt is cooled down. Examples of carriers that form glass solution and suspensions include citric acid [38], sugars such as dextrose, sucrose, and galactose [39], PVP [40], urea [41], and PEG [42].

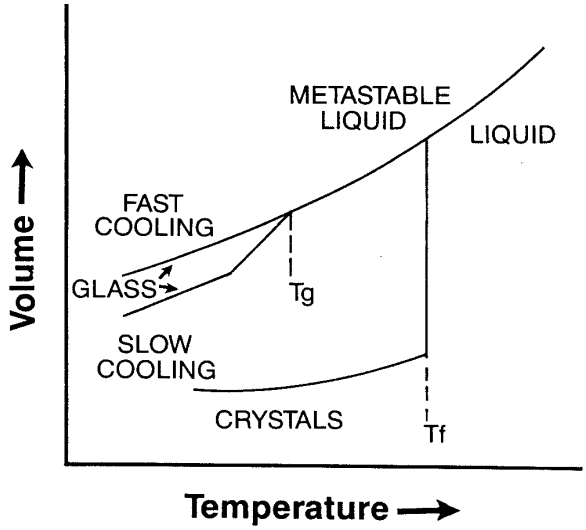

Fig. 6. Volume changes associated with cooling of a melt: T_g is the glass transition temperature and T_f is the melting point of the material

2.3.4 Amorphous Precipitations in a Crystalline Carrier

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. Sulfathiazole was precipitated in the amorphous form in crystalline urea [7]. It is postulated that a drug with a propensity to supercooling has more tendency to solidify as an amorphous form in the presence of a carrier.

2.3.5 Compound or Complex Formation

When the two substances form a molecular compound, it usually gives to a maximum in the phase diagram. An example of this is the quinine-phenobarbital system [30]. It is difficult to generalize the influence of complex formation on dissolution. A complex between digoxin and hydroquinone exhibited a high dissolution rate [43], whereas the insoluble complex between Phenobarbital and polyethylene glycol was shown to reduce both the rates of dissolution and the permeation of Phenobarbital through everted rat gut [44].

2.4 Mechanism of Increased Dissolution Rate

The enhancement in dissolution rate as a result of solid dispersion formation, relative to pure drug, varies from as high as 400-fold [45] to less than two-fold. Corrigan [46] has recently reviewed the current understanding of the mechanism of release from solid dispersions. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

Reduction of particle size: In the case of glass, solid solutions, and amorphous dispersions, particle size is reduced to a minimum level. This can result in an enhanced dissolution rate due to both an increase in the surface area and solubilization. Insight into the relative increase in activity (solubility) on size reduction of a crystal is provided by the Kelvin equation [47].

$$\ln\left(\frac{a}{a_0}\right) = 2\,\gamma\,\frac{\bar{v}}{RTr}$$

Where α/α_0 is the ratio of the activity increase on decreasing a large crystal to a radius r, γ is the average surface free energy of the crystal, and v is the molar volume. It

is necessary for the particles to be in the submicron range in order to see a dramatic change in solubility.

The carrier material, as it dissolves, may have a solubilization effect on the drug. The carrier material may also have an enhancing effect on the wettability and dispersibility of the drug in the dissolution media. This should retard any agglomeration or aggregation of the particles, which can slow the dissolution process.

Formation of metastable dispersions that have a greater solubility would result in faster dissolution rates. A decreased in the activation energy for dissolution was shown for furosemide. The derived energies were 17 kcal per mol for furosemide and 7.3 kcal per mol for the 1:2 furosemide-PVP coprecipitate [48].

2.5 Carriers

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug:

- freely water-soluble with intrinsic rapid dissolution properties,
- non-toxic and pharmacologically inert,
- heat stable with a low melting point for the melt method,
- soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method,
- preferably increase the aqueous solubility of the drug,
- chemically compatible with the drug and not form a strong bonded complex with the drug.

In this PhD work polyethylene glycol have been used as carrier that is why a special attention have been made for its properties. Importance of the carriers in preparation of solid dispersions made the author to mention the other frequently used carriers in this chapter to have a deeper understanding over their role and influences on solid dispersions.

2.5.1 Polyethylene glycol (PEG)

2.5.1.1 General characteristics of PEGs

Polyethylene Glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800-1500 they have a consistency that is best described as Vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formulation of solid dispersions is that they also have good solubility in many organic solvents. The melting points of the PEGs of interest lie under 65 ºC in every case (e.g. the m.p. of PEG 1000 is 30-40 ºC, the m.p. of PEG 4000 is 50-58 ºC and the m.p. of PEG 20000 is 60-63 ºC) [49]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds [50] and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 [51].

2.5.1.2 Influence of the PEG chain length

PEGs of MW 4000-6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50 ºC. If a PEG with too low MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [52]. PEGs with higher MW have also been used with success: products containing PEG 8000 [53] and 10000 [54] showed enhanced dissolution rates compared to the pure drug.

The importance of the carrier to performance of the solid dispersions was illustrated in a study of 14 different drugs formulated as solid dispersions in PEG 6000 [55]. In this study, Dubois and Ford showed that, when the drug is present in a low drug/carrier ratio (<2% in the case of phenylbutazone, up to 15% in the case of paracetamol), the release rate is dependent only on the carrier and not on the drug properties. Results with indomethacin showed similar behavior. Further studies indicated that the release rate is inversely proportional to the chain length of the PEG [56]. Similar results were obtained with etoposide [52] and griseofulvin [10]. However, other studies revealed contradictory behavior. For example, glyburide release from a solid dispersion in PEG 6000 was faster than from a similar dispersion in PEG 4000 [50]. Possible reasons for the better release from PEG 6000 are that the PEG 6000 was able to dissolve more of the drug than the PEG 4000, leading to a greater percentage drug in the molecularly dispersed form, and that the higher viscosity of the PEG 6000 hindered precipitation of the drug following dissolution of the carrier.

A comprehensive study of phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW [56]. When the percentage of drug used was low (0.5-2%), the release followed the rank order PEG 1500>4000>6000>20000, at percentages of 3 and 4% the rank order was PEG 1500>4000>20000>6000 and at a 5% loading the order was 20000>4000>1500>6000. Since the rank order could be clearly correlated with the crystallinity of the solid dispersion, the authors concluded that the release is dependent on the extend to which a molecular dispersion can be formed. On the other hand, contradictory results were obtained with chloramphenicol/PEG solid dispersions, for which the rank order of release was PEG 6000>4000>12000>20000 [57]. In yet other cases, the MW of the PEG had no influence at all on the release rate. For example, Mura et al. [58] showed that 10% dispersions of naproxen in PEG 4000, 6000 and 20000 all exhibited similar release.

2.5.1.3 Influence of the drug/PEG ratio

The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dispersion. If the percentage of the drug is too high, it will form

small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug. Lin and Cham [59] showed that solid dispersions of naproxen in PEG 6000 released drug faster when a 5 or 10% naproxen loading was used than when a 20, 30 or 50% loading was used. These results could be explained on the basis of X-ray diffraction results, which indicated that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline. However, the upper limit to the percentage carrier that can be employed is governed by the ability to subsequently formulate the solid dispersion into a dosage form of administrable size.

2.5.1.4 Drug/PEG systems

Griseofulvin is probably the most studied drug with respect to dispersion in PEGs. Chiou and Riegelman [10] were able to achieve a noticeable increase in the release rate of griseofulvin from solid dispersions in PEG 4000, 6000 and 20000. The fruit of research with PEG/griseofulvin combinations is the marketed product, GrisPEG®. More recent studies with griseofulvin and PEGs have focused on mixtures with various emulsifying agents. Sjökvist et al. [60] introduced small quantities of polysorbate 80, polyethylenedodecylether (Brij® 35), sodium dodecylsulphate (SLS) and dodecylamonium bromide into 10% w/w dispersions of griseofulvin in PEG 3000 and by doing so were able to achieve substantial increases in both the rate and extent of dissolution. Best results were obtained with SLS. Other combination systems, such as a griseofulvin/PEG 6000/talc system [61] could only achieve similar results to that of the two-component dispersion. However, the talc system had the advantages of being easier to process and being less tacky.

An increase in the release rate by formulation as a solid dispersion in PEG 4000 has been observed for many drugs, including oxazepam [62], piroxicam [63] zolpidem [64] and glyburide [50]. In some cases, in vivo data have verified the importance of the increase in release rate to the bioavailability of the drug in question. Arias et al. [65] were able to show that a doubling of the release rate in vitro could be translated into an

increase in the diuretic effect of triamterene in rats. A good correlation between release data from solid dispersions of nifedipine in PEG 6000 and the elimination of the drug in urine was documented in human studies [66]. Similarly, a two-fold increase in the release rate of carbamazepine achieved by formulation as a solid dispersion in PEG 4000 and 6000 was translated into an increase in the bioavailability relative to a suspension of the drug and the marketed product, Tegretol® [67]. However, even better results could be achieved with a hydroxypropyl-β-cyclodextrin complex. Norfloxacin/PEG 6000 solid dispersions also produce a moderate increase in bioavailability [68]. Further drugs, which exhibit elevated release rates when formulated as PEG solid dispersions include Sr33557, a new calcium antagonist [69], ketoprofen [70], oxazepam [71], nifedipine [72], phenytoin [73], ursodeoxycholic acid [74], fenofibrate [75] and prednisolone [76].

There have also been several studies with PEGs of higher MW. Perng et al. [53] achieved a ten-fold increase in the release rate of an experimental 5-lipoxygenase inhibitor with PEG 8000 using a hot melt method. Studies of coevaporate of ibuprofen with PEG 10000, with the talc system and with mixture of the two indicated that the mixture of the PEG with talc produced the best results [54].

2.5.1.5 Problems with PEGs

In general, there are few toxicity concerns associated with the PEGs and they are approved for many purposes as excipients. The low molecular weights of PEGs do, however, tend to show slightly greater toxicity than those of higher molecular weight [49]. In addition, a great number of drugs are compatible with the PEGs. A few cases have been observed in which the PEG proved to have stability problems during manufacture by the hot melt method. A reduction in the PEG chain length was observed for combinations with disulfiram, furosemide, chlorothiazide and chlorpropamide [55]. Another difficulty can lie in the subsequent formulation of the solid dispersion into an acceptable dosage form. If the dispersion is too soft it can be difficult if not impossible to manufacture a tablet dosage form. This is most likely to occur if a PEG with too low a MW is used or if the drug has a plasticizing effect on the PEG [52].

2.5.2 Polyvinylpyrrolidone (PVP)

Polymerization of vinylpirrolidone leads to polyvinylpirrolidone (PVP) of molecular weights ranging from 2500 to 3000000. These can be classified according to the *K* value, which is calculated using Fikentscher' s equation [77]. Table 1 provides an overview of the relationship between the *K* value and the approximate molecular weight of PVP.

The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T_g) is high; for example, PVP K25 has a T_g of 155 ºC [78]. For this reason PVPs has only limited application for the preparation of solid dispersions by the hot melt method. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [79].

Table 1. *K* values of PVP and the corresponding molecular weights [77]

K value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

Polyvinylalcohol (PVA), crospovidone (PVP-CL) and polyvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA) three polymers belong to the polyvinyl group that widely used in solid dispersions [80-83].

2.5.3 Emulsifiers

The release behavior of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are usually used in combination with another carrier. For example, the release of naproxen from solid dispersions in PEG 4000, 6000 and 20000 could be further enhanced when either sodium lauryl sulphate (SLS) or Tween® 80 was added to the system [58]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a solid dispersion to a solid solution. Melts of griseofulvin and PEG 6000 normally contain crystalline areas; in the presence of SLS a solid solution is formed [84].

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [85] demonstrated the ability of bile salts such as cholic acid, deoxycholic acid and lithocholic acid to improve not only the release but also the sedative effects of reserpine when given as a coevaporate. Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters [86].

2.5.4 Other carriers

Many other substances have been tested as carriers for solid dispersions. Table 2 shows a list of materials used as carriers for solid dispersion. In some cases a combination of carriers has been found to be more useful.

Table 2. Materials used as carriers for solid dispersions

Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
Acids	Citric acid, succinic acid
Polymeric materials	Povidone (PVP), polyvinylpolypyrrolidone, polyethylene glycols (PEG), hydroxypropyl-methylcellulose, methylsellulose, hydroxyethylcellulose, cyclodextrines, hydroxypropylcellulose, pectin, galactomannan
Insoluble or enteric polymers	Hydroxypropylmethylcellulose phthalate, Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, deoxycholic acid, Tweens, Spans
Miscellaneous	Pentaerythritol, pentaerythrityltetracetate, urea, urethane, hydroxyalkylxanthins

3. 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 (ME) 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 ME 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 ME were formulated by dropping method and wider investigations were applied for better understanding of the new technology.

4. Materials and methods

4.1 Materials

a) Levodopa (Dihydroxy-fenylanaline, Hungaropharma Ltd., Budapest, Hungary, 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. Polyethylene glycol (PEG) 4000 (Hungaropharma Ltd., Budapest, Hungary, melting range: 50-58 °C) was used as water-soluble carrier for preparation of the solid dispersions.

b) ME was supplied by EGIS Ltd. (Budapest, Hungary, melting range: 258-261 °C). This active agent is an effective NSAID with poorly water-soluble characteristic. All other reagents and solvents were of analytical grade.

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

4.2 Methods

4.2.1 Preparation of solid dispersions

4.2.1.1 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.

4.2.1.2 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.

4.2.1.3 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.

4.2.1.4 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.

4.2.1.5 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 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 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.

4.2.1.6 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.

4.2.1.7 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.

4.2.1.8 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.

4.2.1.9 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).

4.2.1.10 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).

4.2.1.11 Chemometric method

Fiala [87] developed a procedure, correlation analysis, for the XRPD analysis of mixtures of components. Nassab et al. [88. and **III**.] 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) [89,90] can break the data matrix down into profiles (composition profiles and pure diffractogram profiles) with the use of certain constraints [91-93]. Unfortunately, this decomposition is very often not unique because of the rotational and intensity (scaling) ambiguities [90,94]. The rotational ambiguities can be moderated or even eliminated if convenient constraints can be used [91-93]. Tauler et al. [90] developed a Matlab code for MCR-ALS with some constraints. The self - modeling curve resolution (SMCR) method, one of the oldest chemometric procedures, was introduced for two-component systems by Lawton and Sylvestre [95] 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. [96,97] generalized the LS method for three-component systems with the

same minimal constraints. Rajkó et al. [98] 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 for Meloxicam investigations.

4.2.1.12 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 [99]. Contact angles can be determined with *Drop Shape Analyzers* [100]. Figure 7. shows contact angles of water on different surfaces.

water on glass water on teflon water on steel

Fig. 7. Contact angles of water on different surfaces

This is the *wetting* phenomenon, which can be explained by the interaction between interfaces, by the surface free energy, and it is also influenced by adsorption and the liquid properties [101-102]. The most important parameter of wetting is the contact angle (Θ = theta) (Fig. 8.).

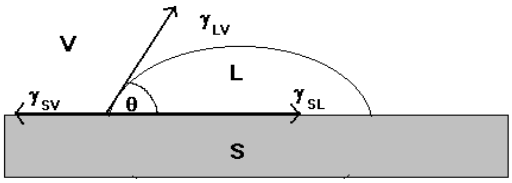

Fig. 8. Contact angle (Θ) between solid surface and liquid

where: γ_{SV} = interfacial tension between solid surface and vapor, γ_{SL} = interfacial tension between solid surface and liquid, γ_{LV} = interfacial tension between liquid and vapor

The thermodynamics of the contact angle is described by the *Young equation* [103]. The behavior of the liquid drop is determined by the interfacial tensions arising among the three interfaces (γ or σ), and according to the Young equation equilibrium arises when the vector sum of the surface forces is zero.

$$\cos\theta = \frac{\gamma_{sv} - \gamma_{sl}}{\gamma_{lv}}$$

The Young equation

Theoretical relationships by Owens et al. [104]

The interfacial tension of a liquid (γ_l) results from the polar (γ_l^p) and disperse (γ_l^d) component of interfacial tension (1). The same applies to the interfacial tension of a solid phase (γ_s) (2).

$$\gamma_l = \gamma_l^d + \gamma_l^p \qquad \gamma_s = \gamma_s^d + \gamma_s^p \tag{1), (2}$$

The interfacial tension between the solid surface and the liquid drop can be calculated with (3), (4):

$$\gamma_{sl} = \gamma_s + \gamma_l - 2\left(\sqrt{\gamma_s^d \cdot \gamma_l^d} + \sqrt{\gamma_s^p \cdot \gamma_l^p}\right) \tag{3}$$

$$\cos\Theta = f\left(\gamma_s, \gamma_s^d, \gamma_l, \gamma_l^d\right) \tag{4}$$

If the contact angles and the γ_l^p and γ_l^d (from data base) of test fluids are known, x-y pairs can be composed according to the above equations (5), (6):

$$\sqrt{\frac{\gamma_l - \gamma_l^d}{\gamma_l^d}} = \sqrt{\frac{\gamma_l^p}{\gamma_l^d}} = x \qquad \frac{1+\cos\theta}{2} \cdot \frac{\gamma_l}{\sqrt{\gamma_l^d}} = y \tag{5), (6}$$

It leads to the ***y = mx + b*** line equation, and from this the surface free energy can be calculated (7), (8):

$$\gamma_s^p = m^2 \text{ and } \gamma_s^d = b^2 \quad (7)$$

$$\downarrow\downarrow$$

$$\gamma_s = \gamma_s^d + \gamma_s^p \quad (8)$$

5. Results and discussion

In the melt solidification technology (special hot melt technology) an important parameter, which influences the shape of the produced sample, is the surface free energy of the cooling surface. The surface free energy determines the contact angle between the drop and the cooling plate and if the melt-drop keeps its drop shape or flows on the surface during the solidification time. Three different surfaces such as enamel, steel and teflon were tested and the surface free energies calculated [105] (Table 3.).

Table 3**.** The surface free energies of the tested surfaces

Surface material	**Line equation**	**γ_s^p (mN/m)**	**γ_s^d (mN/m)**	**Surface free energy (mN/m)**
Enamel	y = 4.958x + 5.1569	24.58	26.63	**51.21**
Steel	y = 2.2003x + 4.9999	4.84	24.90	**29.73**
Teflon	y = 2.0393x + 3.8067	4.18	14.44	**18.61**

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.

5.1 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 [106. and **I**.].

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 two methods, particularly during the first 20 minutes (Fig. 9.). Another aspect of preformulation studies was to investigate the applicability of the dropping method to produce spherical particles.

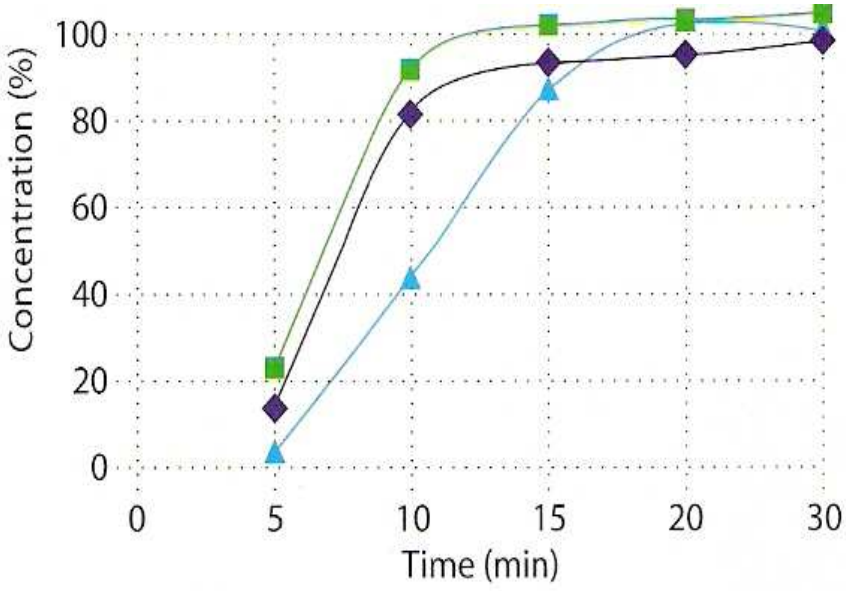

Fig. 9. Comparison of dissolution rates of solid dispersions produced by three methods. ■ Series 1: samples made by dropping method. ♦ Series 2: samples made by direct capsule filling method. ▲ Series 3: samples made by conventional method

Result of the DSC investigation (Fig. 10.) of pure levodopa (C) shows the decomposition prior to melting at 281 °C. In case of the samples, which contain PEG 4000 (A and B) 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 (B) lower energy is

required to initialize the melting process of the levodopa. Sample B normalized at –117.54 Jg $^{-1}$, sample A normalized at –120 Jg $^{-1}$ and pure Levodopa normalized at –529.54 Jg $^{-1}$. 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.

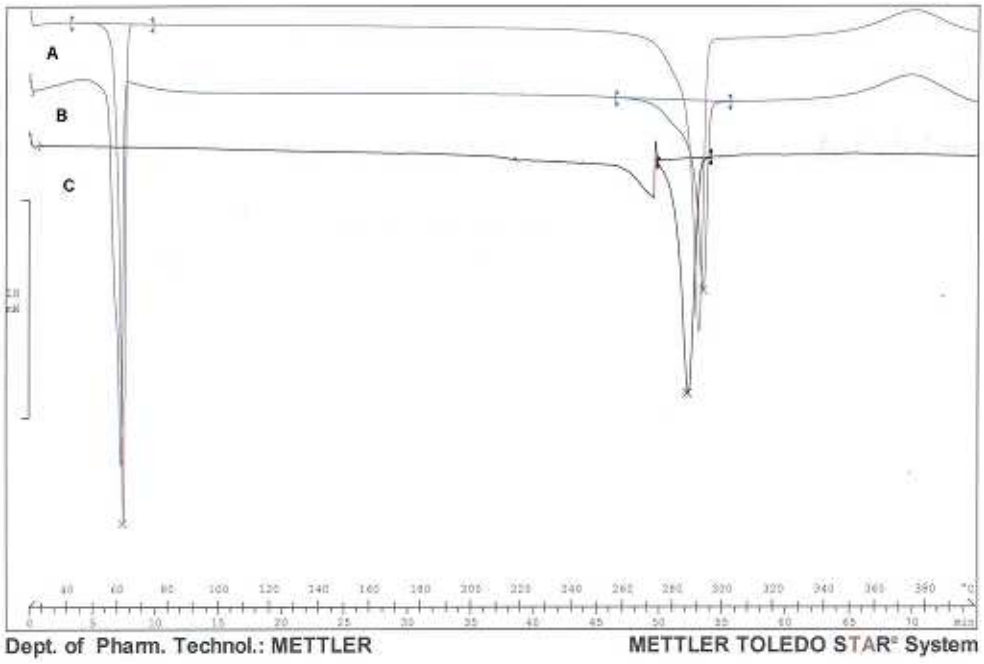

Fig. 10. DSC investigation of PEG 4000-levodopa physical mixture (A), PEG 4000-levodopa prepared by melting method (B) and pure levodopa (C)

Structural changes of Levodopa crystals in different samples were investigated by XRPD (Fig. 11.). XRPD investigation shows that Levodopa crystals were changed when blended with PEG 4000. Some of the peaks appeared in the diffractogram of pure levodopa (11.a) disappeared in diffractograms of the samples where levodopa was blended with PEG 4000. Furthermore, samples prepared by dropping method (11.b) show fewer peaks than the samples prepared by physical mixture (11.c). 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.

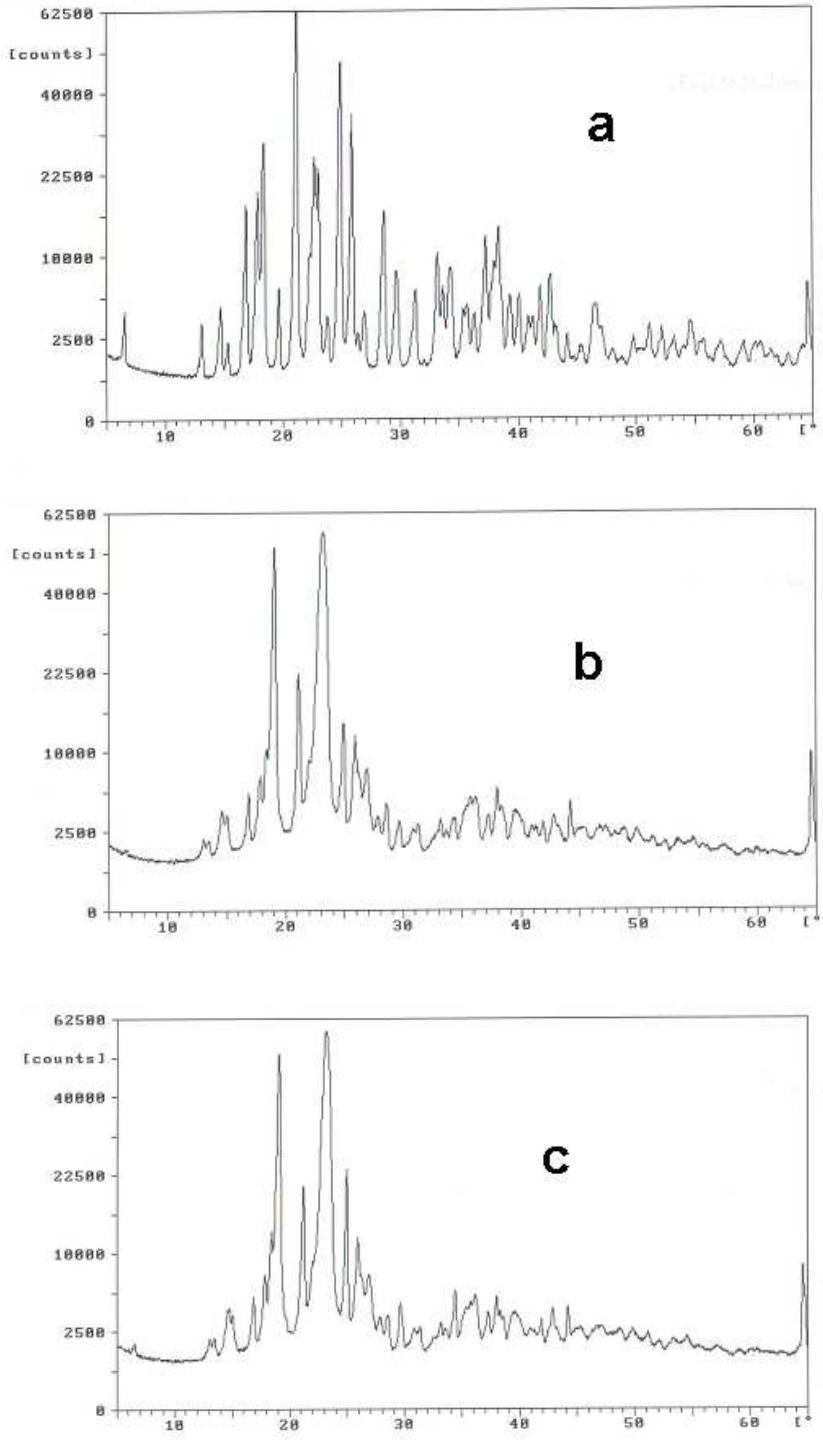

Fig. 11. XRPD investigation of pure Levodopa (a), sample made by dropping method (b) and physical mixture (c)

This results show that among three applied melt processing methods the spherical particles developed by dropping method have better drug release properties than other two methods. Figure 12. shows a batch of Levodopa-PEG 4000 round particles with 2.5 mm (± 13mm) in diameter produced by dropping method.

Fig. 12. A batch of Levodopa-PEG 4000 round particles prepared by dropping method

Difficulties such as pulverization, sifting and compressibility encountered with the other methods are avoided by producing spherical particles using dropping method. On the other hand the dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. Spherical particles can be used as dosage form or it can be filled into capsules. Figure 13. shows different melt processing methods for solid dispersions.

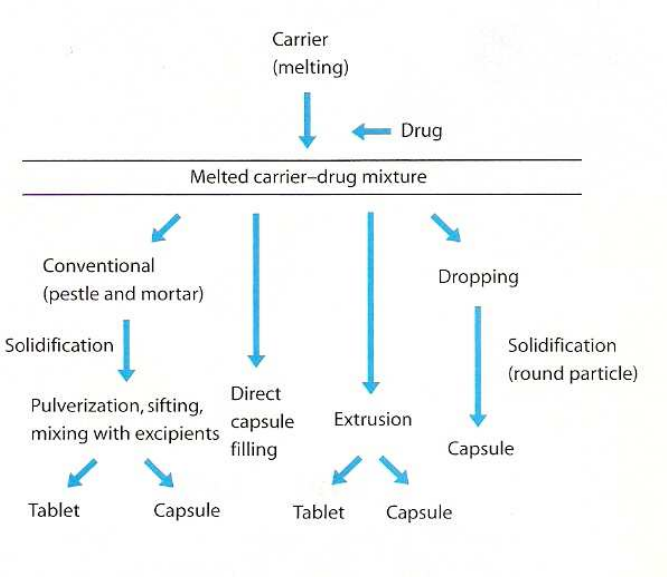

Fig. 13. Different processing methods for solid dispersions

Promising results in preformulation studies for Levodopa-PEG 4000 solid dispersions encouraged us to apply the dropping method on Meloxicam a poorly water-soluble drug to investigate the reproducibility and applicability of this technology and wider investigations were applied for better understanding of this new technology. The results of these investigations are presented as follow.

5.2 Results and discussion 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 [106. and **I**.].

In the dropping method, the temperature of the melted drug-carrier mixture was 58 °C, which is determined by the melting point of PEG 4000. The surface energy of the

plate onto which the melt is dropped is an important factor in the production of round particles of the ME - PEG 4000 solid dispersion.

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 components and the parameters of the investigated samples are summarized in Table 4.

Table 4. Parameters of investigated samples and pure ME

Sample	Composition	Dosage form	Characteristic parameters
S1 (physical mixture)	15 mg ME and 45 mg PEG 4000	Capsule, no. 2	-
S2 (tablet)	15 mg ME and 45 mg PEG 4000	Tablet (pressed from physical mixture)	Height: 1.83 mm (STDEV ± 0.05 mm) Crushing strength: 35.7 N (STDEV ± 5 N) Diameter of tablet: 10 mm
S3 (round particle)	5 mg ME and 15 mg PEG 4000 for 1 solid drop	Capsule, no. 2. with 3 round particles	Diameter of particles: 2.75 mm (STDEV ± 0.12 mm)
ME (pure)	15 mg ME	Capsule, no. 2.	-

The rates of dissolution of the above - mentioned three samples and pure drug were measured and are shown in Figure 14, 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).

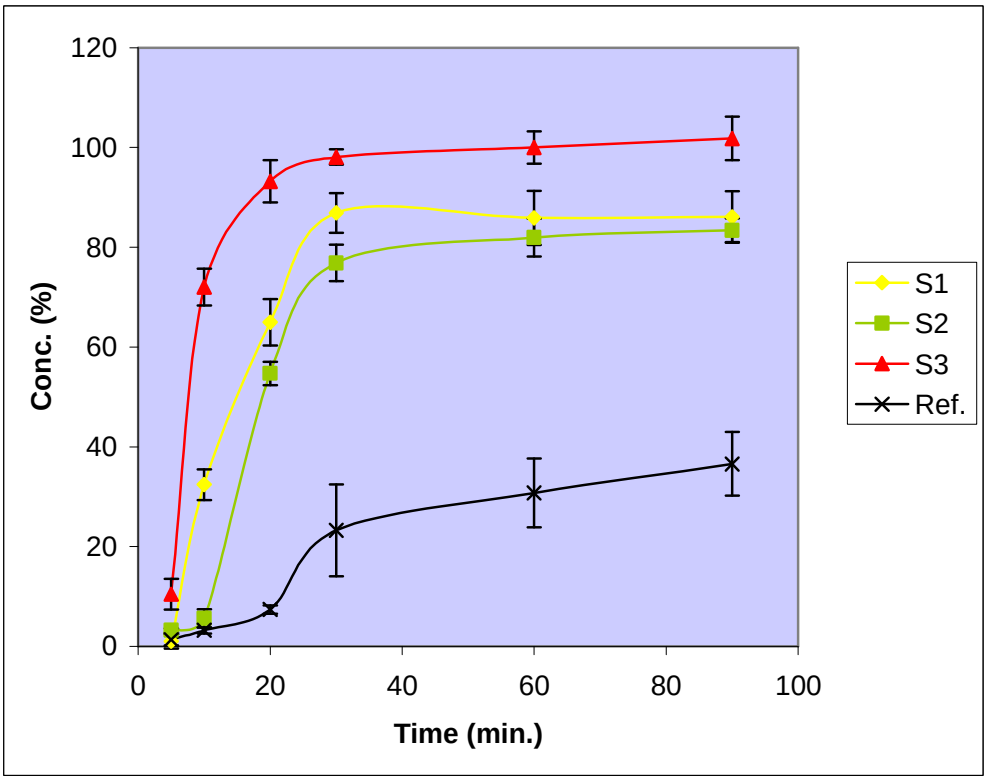

Fig. 14. Rates of dissolution of different samples. Ref.: pure ME, S1: physical mixture, S2: tablet, S3: round particles developed by dropping method

The sequence of the rates of dissolution of the samples was: round particle (S3) > physical mixture (S1) > tablet (S2) > pure ME. The effect of the high specific surface area of ME was not manifested because of the tendency of the small (~ 6 µm) crystals to agglomerate. After dissolution of the capsule, the particles that were very hydrophobic formed clusters in the artificial enteric juice. This was demonstrated by the rate constant (k = 0.1795) of the dissolution of ME, which was calculated for modified Langenbucher function (Table 5.). The three samples (round particles, physical mixture and tablet) dissolved faster and the differences between these curves can be characterized by the rate constants (k) according to the modified Langenbucher function.

Table 5. Characteristic Langenbucher function values of the investigated samples

Sample	k (rate constant)	n (intercept)	R^2
S1 (physical mixture)	0.1818	0.2604	0.8822
S2 (tablet)	0.1776	0.3041	0.9128
S3 (round particle)	0.3868	0.5700	0.9961
ME (pure)	0.1795	0.0693	0.9519

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 samples (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. 15. and 16.). 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.

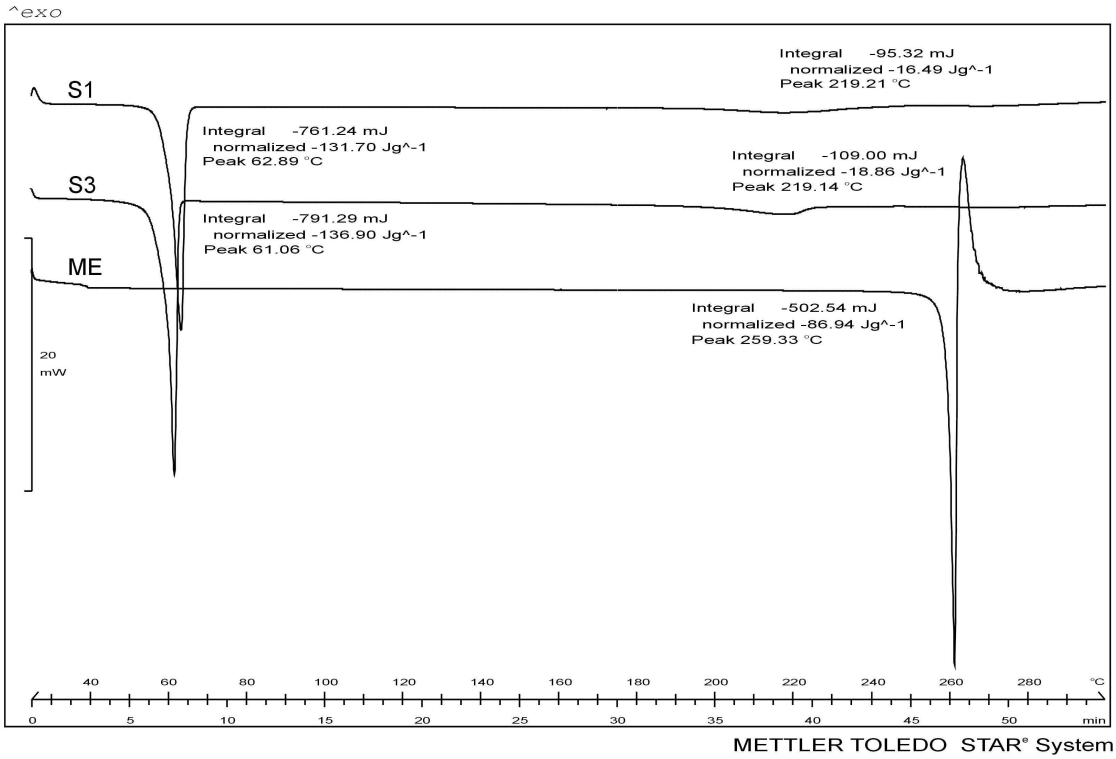

Fig. 15. DSC curves of pure ME, physical mixture (S1) and round particles made by the dropping method (S3) at heating rate of 5 °C/min

In Figure 16, the DSC investigations were applied at heat rate of 30 °C/min to obtain sharper peaks and more information to differentiate the crystal habit of three samples. Thermogram of figure 16 shows that less energy is needed to reach the melting point of the samples made by dropping method (S3), which means that less amount of ME is present in crystal form. It can be concluded that more ME were dissolved in S3 than other samples, which promotes better dissolution properties.

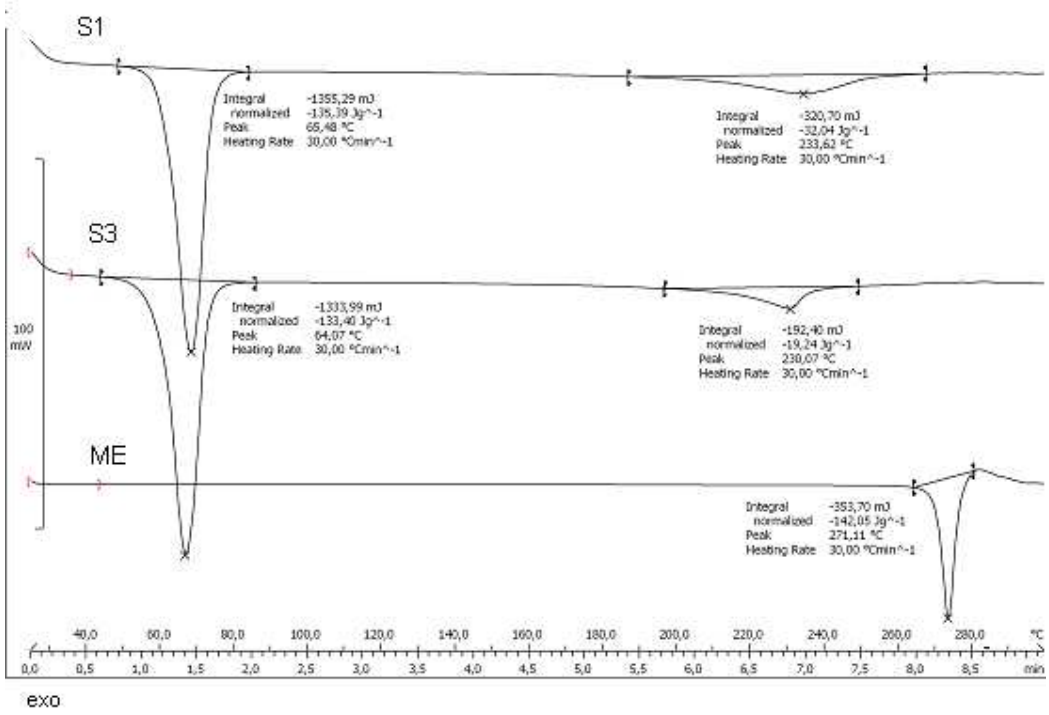

Fig. 16. DSC curves of pure ME, physical mixture (S1) and round particles made by the dropping method (S3) at heating rate of 30 °C/min

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. 17.). 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.

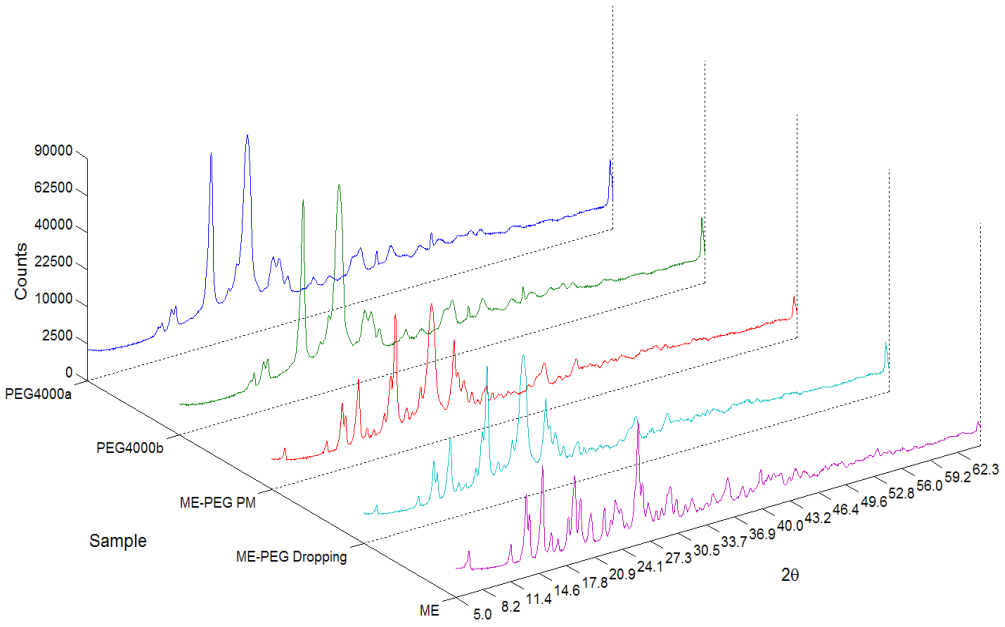

Fig. 17. X-ray powder diffraction. Starting material: ME (pure), PEG 4000a (untreated, commercial) and PEG 4000b (melted and solidified). Samples: S1 - physical mixture (ME - PEG PM), S3 - round particle (ME - PEG dropping)

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. The Borgen plot (Fig. 18.) of the transformed diffractograms revealed that points 1 and 2 of the inner polygon are very close to each other, because they are the transformed parallel diffractograms of PEG 4000a and PEG 4000b. Points 3 (S1) and 4 (S3) are farther from each other, which mean that the dissimilarity is larger than that for the two kinds of PEG 4000. In Figure 19., 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. Figure 20.

depicts the estimated bands given by using these constraints. It can be concluded that the content

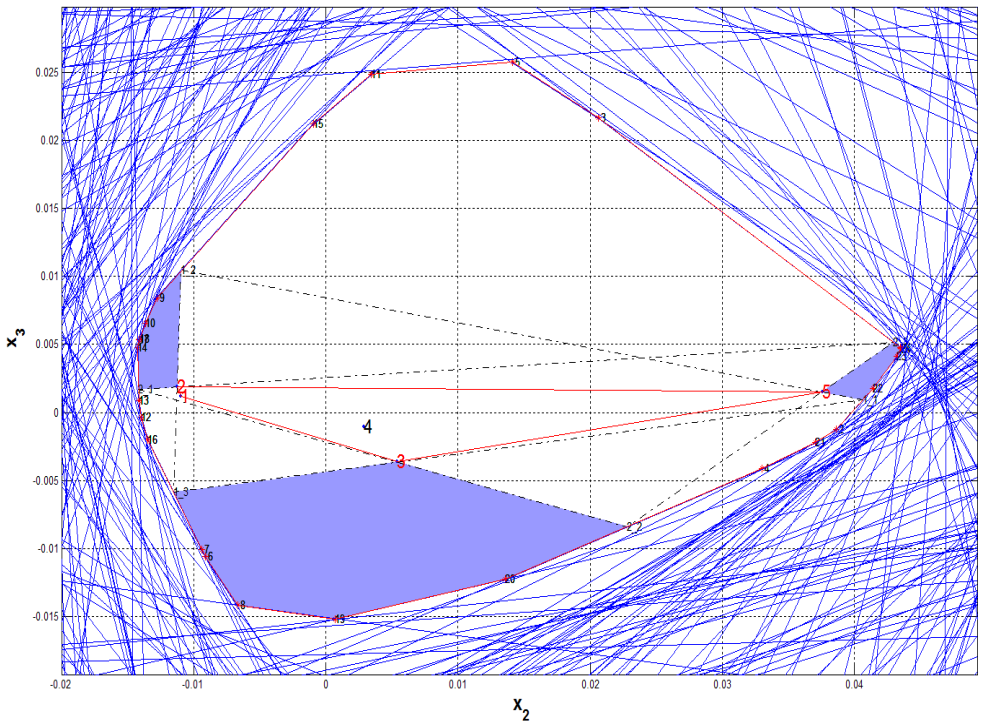

Fig. 18. Borgen plot of the transformed diffractograms. There are 5 points in or on the inner polygon according to the 5 samples shown in Fig. 17

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 may be as follows. 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.

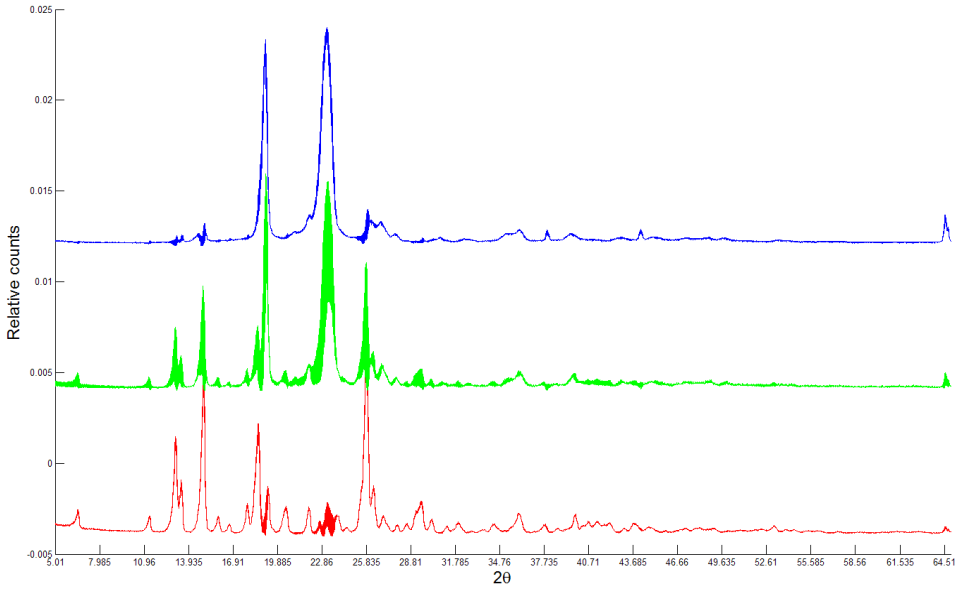

Fig. 19. Diffractograms of the three components given by the SMCR method. Blue band (1): PEG 4000; red band (2); ME; green band (3): a new mixed crystal form

This is connected with the partial dissolution of the ME in the melted PEG 4000 (Fig. 15. and 16., DSC scan) 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.

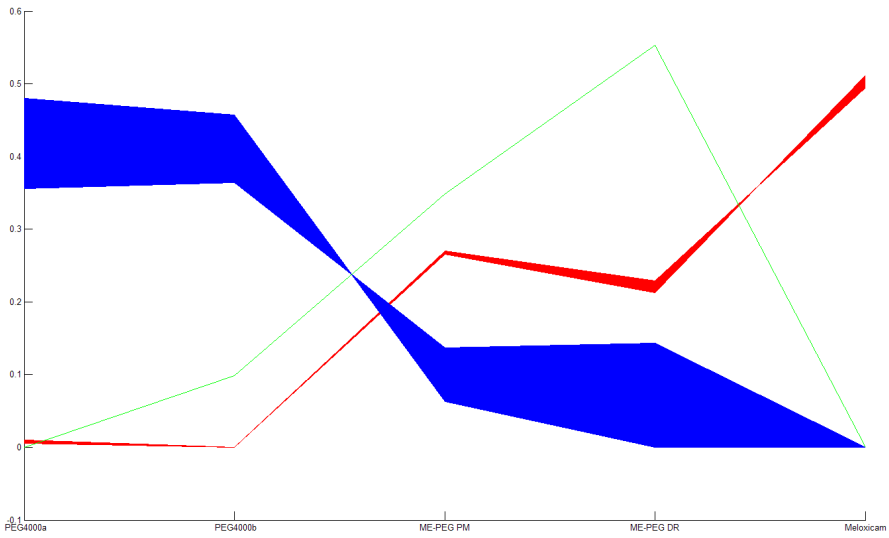

Fig. 20. Compositions of the samples given by using the SMCR method and the constraints detailed in the text. Blue band (1): PEG 4000; red band (2): ME; green band (3): the new mixed crystal form

5.3 Conclusion

It can be concluded that the dropping method is a viable technology with which to produce solid dispersions of Levodopa and ME in a single step by dropping the melted drug-carrier (PEG 4000) mixture so as to form spherical particles. These round particles can be filled into hard gelatin capsules or used as final dosage form. The dropping method does not involve the use of organic solvents, and therefore has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Although there is still much work to do in this field (uniformity and stability), the dropping method appears to be a promising procedure for the formulation of solid dispersions. Simplification of the formulation process may overcome the manufacturing difficulties [107. and **II**].

6. 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. 21.).

Protocol of dropping method

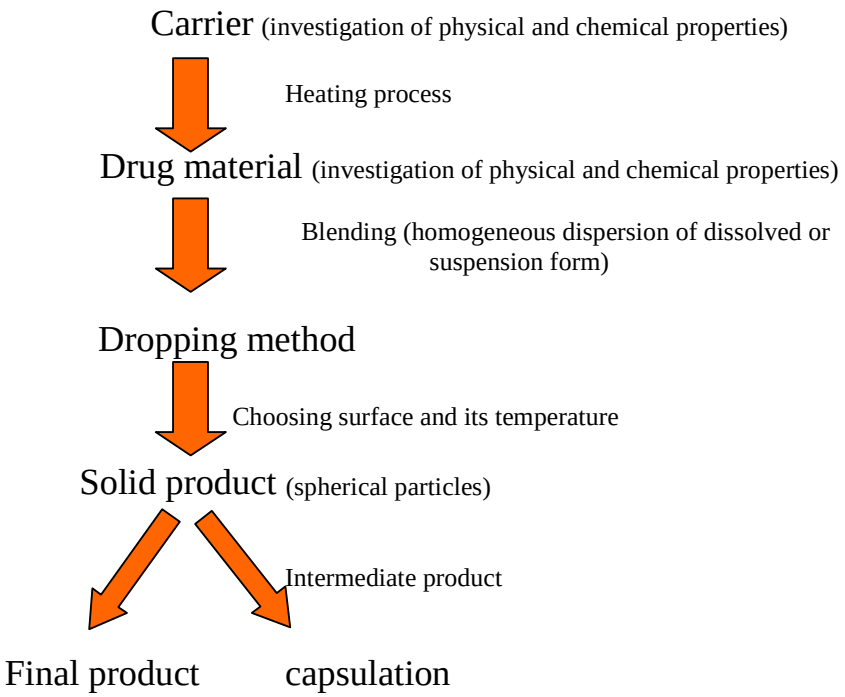

Fig. 21. Formulation of solid dispersion by dropping method

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.

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