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# VPLIV INTRINZIČNE VISKOZNOSTI IZHODNE POLIMERNE RAZTOPINE NA LASTNOSTI DELCEV POLIVINILACETATA, PRIDOBLJENIH S SUŠENJEM Z RAZPRŠEVANJEM

# CORRELATION BETWEEN INTRINSIC VISCOSITY OF DIFFERENT POLYVINYL ACETATE SOLUTIONS AND PARTICLE PROPERTIES OF SPRAY DRIED SOLID DISPERSION

Ljubljana, 2014

My master thesis studies were done within the study exchange at the University of Copenhagen. I was positioned as a master student at the Pharmaceutical technology group at the department of Pharmaceutics and Analytical chemistry at the Faculty of pharmaceutical sciences Copenhagen. My mentor was prof. dr. Stanko Srčič and my comentor was prof. dr. Stefania G. Baldursdottir. Prof. dr. Mingshi Yang and dr. Jari Pajander were also highly involved in the study.

Diplomsko nalogo sem opravljala v okviru študijske izmenjave na Univerzi v Kopenhagnu. Sodelovala sem v skupini za farmacevtsko tehnologijo, Katedre za farmacetsko tehnologijo in analitsko kemijo na Fakulteti za farmacijo, Univerze v Kopenhagnu. Diplomsko delo sem izdelala pod mentorstvom prof. dr. Stanka Srčiča ter pod somentorstvom Stefanie G. Baldursdottir, v tesnem sodelovanju s prof. dr. Mingshi-jem Yang-om ter dr. Jari-jem Pajander-jem.

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**Statement**

Hereby I declare that I have prepared this master thesis independently under supervision of prof. dr. Stanko Srčič. and dr. Stefania G. Baldursdottir.

**Izjava**

Izjavljam, da sem diplomsko delo izdelala samostojno pod mentorstvom prof. dr. Stanka Srčiča in somentorstvom prof. dr. Stefanie G. Baldursdottir.

Špela Zakšek

Ljubljana, March 2014

# CONTENT

## ABSTRACT

The use of different solvents to dissolve the polymer has an important effect on the rheological properties of polymers thus the conformation of the polymer differ regarding to the polymer-polymer and polymer-solvent interactions in the given solvent. In the present study the viscosimetric behaviour of polyvinyl acetate (PVAc) in various solvents was thoroughly investigated. The intrinsic viscosity values of the polymer in methanol, acetone and different methanol-acetone mixtures have been computed from the experimental values. It has been revealed that intrinsic viscosity of the polyvinyl acetate has the highest value in the methanol-acetone 1:5 mixture and the lowest in the pure methanol of all the investigated solvents, indicating that the polymer is in extended form when it is dissolved in methanol-acetone 1:5 mixture and it is folded when it is dissolved in pure methanol.

Furthermore in this study the impact of the polymer conformation on characteristics of not only pure polymer spray dried particles but also on solid dispersion particles has been studied using celecoxib (CEL) as a drug. This cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drug (NSAID) is classified to the class II of Biopharmaceutical classification system (BCS) indicating that it has low water solubility but high permeability.

The scanning electron microscopy (SEM) pictures revealed difference between the particles spray dried from different solvents indicating that the conformation of the polymer has the important effect on the particles morphology.

Solid state stability study of the solid dispersion particles was performed using X-ray powder diffraction (XRPD), Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy. The results obtained from X-ray powder diffraction showed the transition of crystalline nature of the pure drug to the amorphous form in solid dispersion, while the Fourier transform infrared spectroscopy studies and Raman spectroscopy studies demonstrated the absence of drug-polymer interactions, thus stabilization of the amorphous form of the drug.

In the present study the dissolution profile of the pure crystalline drug and solid dispersion were investigated and as it has been expected it was found out that the dissolution of the drug is prolonged when solid dispersion made up with celecoxib and polyvinyl acetate is tested.

According to the results obtained many new interesting questions appeared, regarding the possibility that drug might be dispersed in different degree in the solid dispersion due to different PVAc conformational structure, then resulting in different solid state stability.

## POVZETEK

Uporaba različnih topil za raztapljanje polimerov ima pomemben vpliv na reološke lastnosti le-teh. Oblika polimera v raztopini je namreč odvisna od interakcij polimer-polimer ter interakcij polimer-topilo. V diplomski nalogi smo najprej preučili viskozimetrične lastnosti polimera polivinilacetata v različnih topilih. Iz dobljenih vrednosti kinematične viskoznosti smo preračunali vrednosti intrinzične viskoznosti polivinil acetata v različnih deležih topil, metanola, acetona in etanola. Ugotovili smo, da ima najvišjo intrinzično viskoznost raztopina polivinilacetata v mešanici metanola in acetona v razmerju 1:5, najnižjo vrednost pa smo izračunali za polimer raztopljen v metanolu. Iz dobljenih rezultatov lahko sklepamo, da je molekula polivinilacetata v mešanici topil v raztegnjeni obliki, medtem, ko je molekula v metanolu zvita.

V nadaljevanju študije smo preučili vpliv oblike polimera na lastnosti delcev samega polimera ter na lastnosti trdne disperzije polimera in zdravilne učinkovine – celekoksiba, pridobljenih z metodo sušenja z razprševanjem. Celekoksib spada med COX-2 selektivne nesteroidne antirevmatike in ga glede na Biofarmacevtski klasifikacijski sistem uvrščemo v razred II, kar pomeni, da je slabo topen v vodi, ima pa dobre permeabilnostne lastnosti.

Na posnetkih, pridobljenih s pomočjo elektronskega mikroskopa, se lepo opazijo razlike v obliki delcev pridobljenih s sušenjem z razprševanjem iz raztopin, kjer so bila uporabljena različna topila. Ti rezultati dokazujejo, da ima oblika polimera v vhodni raztopini za sušenje z razprševanjem pomemben vpliv na obliko končnih delcev, ki jih s to metodo pridobimo.

Izvedli smo tudi študijo stabilnosti s pomočjo različnih metod, in sicer rentgenske difrakcije, Fourierjeve transformacije ter ramanske spektroskopije. Iz difraktogramov rentgenske difrakcije je razvidno, da je v trdni disperziji celekoksib v amorfni obliki, poleg tega pa je iz spektrov, ki smo jih pridobili z Fourierjevo transformacijo ter iz Raman spektrov razvidno, da so med zdravilno učinkovino in polimerom nastale interakcije, kar ima posledično tudi pomemben vpliv na stabilnost polimera.

Poleg prej omenjenega smo se osredotočili tudi na preskus sproščanja zdravilne učinkovine iz trdne disperzije. Ugotovili smo, da so vrednosti raztopljene učinkovine iz trdne disperzije po določenem času manjše, kot če raztapljamo samo zdravilno učinkovino.

Ugotovili smo da ima oblika polimera v vstopni raztopini pomemben vpliv na obliko zdravilne učinkovine v trdni disperziji ter posledično vpliv na stabilnost zdravilne učinkovine v trdni disperziji in sproščanje le te iz trdne disperzije.

## KEYWORDS

Polyvinyl acetate, celecoxib, solid dispersion, spraydrying, intrinsic viscosity, solid state analysis

## KLJUČNE BESEDE

Polivinilacetat, celekoksib, trdna disperzija, sušenje z razprševanjem, intrinzična viskoznost, analiza trdnih delcev

# LIST OF ABBREVIATIONS USED/ SEZNAM KRATIC

**Table I:List of abbreviations**

| **ABREVIATION/ KRATICA** | **English** | **Slovenian** |
|---|---|---|
| API | Active pharmaceutical ingredient | Zdravilna učinkovina |
| BCS | Biopharmaceutical classification system | Biofarmacevtski klasifikacijski sistem |
| CEL | celecoxib | celekoksib |
| COX-2 | cyclooxgenase-2 | ciklooksigenaza-2 |
| FTIR | Fourier transform infrared spectroscopy | Fourierjeva transformacija |
| GPC | gel permeation chromatography | gelska izključitvena kromatografija |
| MeOH | methanol | metanol |
| NSAID | nonsteroidal anti-inflammatory drug | nesteroidni antirevmatik |
| PBS | Phosphate buffer system | Fosfatni puferski sistem |
| PVAc | polyvinyl acetate | polivinilacetat |
| SEM | scanning electron microscopy | elektronska mikroskopija |
| SLS | Sodium lauryl sulphate | Natrijev lavrilsulfat |
| TGA | thermogravimetric analysis | termogravimetrična analiza |
| XRPD | X-ray powder diffraction | rentgenska difrakcija |

# 1. INTRODUCTION

## 1.1 POLYMERS

Polymers are large molecules made up of many small repeating units, called monomers. By regulation of the molecular weight of polymer and by modification of its composition - by blending them with other polymers or making new copolymers, the physical and mechanical properties of these large molecular weight materials can be designed and thus polymers can be adjusted for a given application (1, 2).

Synthetic and natural based polymers together with their derivatives are widely used in pharmaceutical industry. With the progress in polymer chemistry and technology, high biocompatible polymers were developed. Nowadays they have an important role in pharmaceutical applications. In oral delivery, they are used as coating film, binders, taste masking materials, protective agents, drug carriers and release controlling agents (1). In addition specific polymers could protect drugs during their passage through the acidic environment of the stomach (1). Polymers are included also in the formation of the transdermal patches as backings, adhesives or drug carriers in matrix or membrane products. Biodegradable polymers have been largely used to provide controlled release of proteins and peptides (1). Moreover in biomedicine polymers have been used to develop devices for controlling drug delivery or for replacing failing natural organs (2).

### *POLYVINYL ACETATE*

In our study we focused on the most widely used vinyl ester polymer, not only in the field of pharmaceutical technology but also in adhesives, paint, paper and textile additive industries (3). Polyvinyl acetate, is synthetically prepared from the corresponding monomer of vinyl acetate using free-radical polymerization also known as chain polymerization or addition polymerization. A vinyl acetate monomer is used to manufacture not only homopolymers but also copolymers (3).

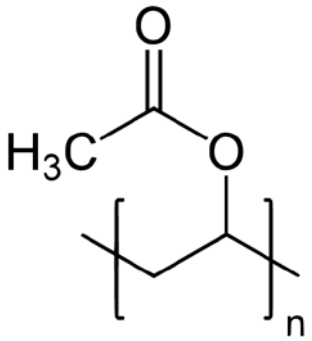


**Figure 1: Chemical structure of polyvinyl acetate**

Polyvinyl acetate is an amorphous, non-crystalline, thermoplastic polymer. It is used either as an intermediate for the production of polyvinyl alcohol and polyvinyl phthalate which, due to unstable monomers cannot be prepared by direct polymerization, or as an excipient in different drug delivery systems (3).

The density of breads of polyvinyl acetate used in our study (average Mw ~100,000 by GPC) (4) is 1.18 g/cm$^3$ at 25°C (4) and it decreases with an increase in the temperature. The glass transition temperature ($T_g$) of polyvinyl acetate depends on the molecular weight of the polymer. The higher the molecular weight, the higher $T_g$ is obtained. For medium molecular weight polyvinyl acetate, $T_g$ varies between 28–31°C and is also found to be 34–39°C when polyvinyl acetate is completely dry, and less than 30°C when it is wet (3). For easier understanding of some phenomena occurring in our study it is important to know also that amorphous polymers are hard, stiff and glassy at the temperatures below the $T_g$ and on the contrary they are rubbery and may flow at the temperatures well above the $T_g$. Amorphous polymers are also known to soften over a wide temperature range (2). Melting range of polyvinyl acetate has been reported to range from 70°C to 115°C (4).

Furthermore due to its high flexibility and low toxicity polyvinyl acetate is widely used in food industry as a base for chewing gum and for coating fruits and vegetables. In pharmaceutical industry polyvinyl acetate is used as coating material to achieve extended drug release, as a part of a copolymer it is used to enhance solubility of water non-soluble drugs (II class of BCS) by producing solid dispersions (5-8) good example for that is vinyl pyrrolidone – vinyl acetate copolymer (9). It is also used to produce extended release formulations in the form of matrix tablets. Additionally some studies using PVAc for preventing the bitter taste and side effects of orally disintegrating tablets of ibuprofen has been made (10).

### 1.2. VISCOSITY OF POLYMER SOLUTIONS

Viscometry of dilute solutions, which are defined below, is an important method to characterize polymers. The instrument used is cheap and viscosity techniques are experimentally simple, which gives a significant advantage to the method. With the knowledge of the viscosity of polymer solution, molar mass, polymer size, polymer branching, chain flexibility and temperature dependence can be determined (11). Furthermore, investigation of viscosity and volume effects on mixing of polymer and solvent can be a powerful tool for the characterization of inter- and intramolecular interactions present in the polymer – solvent mixtures (11). Those depend upon the polymer molecular structure, chemical composition, solution concentration, solvent molecular structure and solution temperature. In addition to polymer research, polymer-solvent mixture viscosity is an important physical property also in polymer development and engineering (12).

Classical viscometric measurements are performed using a capillary viscosimeter – Ubbelohde, Ostwald. Also in our study, the viscosity of the polymer solutions was measured using capillary, Ubbelohde viscosimeter, calibrated by water.

The measured quantity when using a capillary viscosimeter is the specific viscosity ($\eta_{sp}$) or relative viscosity ($\eta_{rel}$):

$$\eta_{sp} = \frac{\eta - \eta_0}{\eta_0} = \frac{t - t_0}{t_0} = \eta_{rel} - 1 \qquad \text{(equation } \textit{1}\text{)}$$

Where η and $\eta_0$ are the viscosities of dilute polymer solution and pure solvent, respectively. In practice, time needed for a certain volume of the solvent ($t_0$) or solution (t) to flow from one mark to the other is measured. The specific viscosity is actually the fractional increase in the viscosity over that of the pure solvent, caused by the addition of the polymer, and according to Einstein it is proportional to the volume fraction of a polymer in solution.

Further specific viscosity is divided by concentration and another quantity of interest is provided, reduced viscosity also known as viscosity number (11).

$$\eta_{red} = \frac{\eta_{sp}}{\mathrm{c}} \qquad \text{(equation } \textit{2}\text{)}$$

In the limit of infinite dilution, the reduced viscosity is known as the intrinsic viscosity [η].

$$[\eta] = \lim_{\mathrm{c}\to 0} \frac{\eta_{sp}}{\mathrm{c}} \qquad \text{(equation } \textit{3}\text{)}$$

The intrinsic viscosity, also called »the limiting viscosity number« is a parameter characteristic for a given polymer in a given solvent at a certain temperature, it depends on the size and shape of the polymer molecule but it is independent on the polymer concentration. Furthermore it is the inherent ability of a substance to give viscosity to a solution (13).

The concentration dependence of the specific viscosity was described by Huggings (11), who found that the slope of the $\frac{\eta_{sp}}{\mathrm{c}}$ versus c curve, $k$, depends on molecular weight of the polymer. This dependence is described by the Huggins equation (equation *4*), where c is the concentration (g/mL or g/dL), $k_H$ is the Huggins constant for a given polymer, solvent and temperature and $[\eta]$ is the intrinsic viscosity.

$$\frac{\eta_{sp}}{\mathrm{c}} = [\eta] + k_H[\eta]^2\mathrm{c} \qquad \text{(equation } \textit{4}\text{)}$$

The plot of $\frac{\eta_{sp}}{\mathrm{c}}$ in dilute solutions is often linear. For polymers in thermodynamically good solvents, $k_H$ usually has a value around 1/3, while larger values of 0,5-1 are typical for poor solvents.

An alternative equation was proposed by Kraemer (equation *5*) (14), where $k_K$ is the Kraemer constant.

$$\ln \frac{(\eta_{sp}+1)}{c} = [\eta] + k_K[\eta]^2 c \qquad \text{(equation } 5\text{)}$$

For polymers in good solvents $k_K$ is a negative value. The most accurate procedure to determine intrinsic viscosity with Huggins and Kraemer equations is to plot according to both equations (equation *4* and equation *5*) and to take the mutual intercept as intrinsic viscosity.

In a good solvent, the polymer molecules with high molecular weight typically expand to form spherical coils. Hydrodynamic volume of those coils depends upon the polymer molecular weight and its thermodynamic interactions with the solvent. When there are more polymer – solvent interactions than polymer – polymer interactions the hydrodynamic volume of the polymer coil increase, the polymer expands, and when the polymer – solvent interactions are unfavourable hydrodynamic volume of the polymer decrease and the polymer coils up (11).

Important aspect to predict swelling of given polymer in different solvents is also by knowing the values of Hildebrand and Hansen solubility parameters. There are various experimental techniques which are used to measure solubility parameters. It is known from the previous studies that there is correlation between Hansen solubility parameter and intrinsic viscosity, therefore Hansen solubility parameter of a polymer could be calculated from its intrinsic viscosity in a given solvent (15).

The Hildebrand solubility parameter is an estimate of the degree of interactions between materials, and is best used to predict solubility of non-polar materials. For pure liquid substance is defined as the square root of the cohesive energy density.

$$\delta = [(\Delta H_v - RT)/V_m]^{1/2} \qquad \text{(equation } 6\text{)}$$

$\Delta H_v$ is the heat of vaporization, and $V_m$ the molar volume. RT is the ideal gas pV term, and it is subtracted form the heat of vaporization to obtain an energy of vaporization.

The Hildebrand solubility parameter (δ) is an estimate of the degree of interactions between materials, and is also best used to predict solubility of non-polar materials. The parameter is derived from the cohesive energy density, which in turn is derived from the heat of vaporization (15). There is a direct correlation between heat of vaporization and the intermolecular forces, such as van der Waals forces and hydrogen bonds. The correlation between intermolecular forces and vaporization could be also translated into a correlation

between vaporization and solubility behaviour, because the same forces have to be overcome to vaporize a liquid to dissolve it (14).

For polymer molecules vaporisation is not possible to be measured therefore series of a given polymer in different solvents are made, and polymer swelling or intrinsic viscosity is measured for the polymer solutions. The polymer is assigned the δ of the solvent providing the maximum swelling coefficient (14).

Further on Hansen proposed an extension of Hildebrand parameter. He divided three major types of interactions in common organic materials. Firstly non-polar interactions, derived from the dispersion forces, defined by the dispersion cohesive energy ($E_D$), the permanent dipole – permanent dipole interactions, which cause the polar cohesive energy ($E_P$) and electron exchange parameter, which relates to hydrogen interactions ($E_H$) (16).

$$E = E_D + E_P + E_H \qquad \text{(equation 7)}$$

If we divide this by molar volume, the sum of the squares of the Hansen D, P and H component equals the square of the total solubility factor ($\delta^2$), which should be equal to the Hildebrand solubility parameter. However for most solvents there are deviations between those two values.

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad \text{(equation 8)}$$

From the previous studies the correlation between the intrinsic viscosity of polymer and solubility parameter of the polymer is known, in *1997 Segarceanu and Leca* (17) deceived a method to calculate the Hansen solubility parameter of a polymer from its intrinsic viscosity in different solvents, which is shown in equations *9*, *10* and *11*. The subscript P is for the polymer and the respective solvents are indicated by an i.

$$\delta_{DP} = \frac{\sum \delta_{Di} \times [\eta]_i}{\sum [\eta]_i} \qquad \text{(equation 9)}$$

$$\delta_{PP} = \frac{\sum \delta_{Pi} \times [\eta]_i}{\sum [\eta]_i} \qquad \text{(equation 10)}$$

$$\delta_{HP} = \frac{\sum \delta_{Hi} \times [\eta]_i}{\sum [\eta]_i} \qquad \text{(equation 11)}$$

Calculation of solubility parameter for polymers is revealed from: $\delta_p = d' \sum G/M'$, where d' is the density of polymer with repeating units of molecular mass M' and G is the molar

attraction constant. Normally without strong interactions like hydrogen bonds, the solubility of a polymer can be predicted if $|\delta_s + \delta_p| < 1$ (18).

Calculation for Polyvinyl acetate is given below (18):

Density = 1,18 g/cm$^{-3}$

Molecular mass of repeating unit is 86,1 g/mol

ΣG = 1,352 J$^{1/2}$cm$^{3/2}$mol$^{-1}$ (1-$CH_3$: 420 J$^{1/2}$cm$^{3/2}$mol$^{-1}$, 1-$CH_2$: 280 J$^{1/2}$cm$^{3/2}$mol$^{-1}$, 1-CH: 140 J$^{1/2}$cm$^{3/2}$mol$^{-1}$, 1-COO: 512 J$^{1/2}$cm$^{3/2}$mol$^{-1}$)

$$\delta_p = \frac{(1{,}18 g/cm^{-3} \text{x } 1{,}352 J^{1/2} cm^{3/2} mol^{-1})}{86{,}1\ g/mol} = \underline{18{,}5\ J^{1/2}cm^{3/2}}$$

Another aspect of our study was to determine the effect of the polymer concentration as well as the apparent viscosity of the feed solution on spray dried particle properties. Therefore different concentration ranges of polymers in the solution should be defined.

c* is the critical overlap concentration characterizes the situation where we get a continuous contact between the polymer coils in the solution (13). c* can be calculated from intrinsic viscosity value (equation *12*).

$$c^* = 1/[\eta] \qquad \text{(equation } 12\text{)}$$

That means that viscosity of all the samples prepared at c* is equal. Therefore spray dried particles which are spray dried from solutions made by different solvents but with the same viscosity values could be also compared.

Further on a dilute solution is where the solution concentration is below c*, there is not a continuous contact between the polymer molecules. Semi-dilute solution is when the concentration of polymer is larger than c*, and the polymer molecules are in continuous contact with each other. And when the concentration of polymer is so high that we have an uniform distribution of polymer segments among the solvent molecules (c > c**) we get a concentrated solution (figure 2) (13).

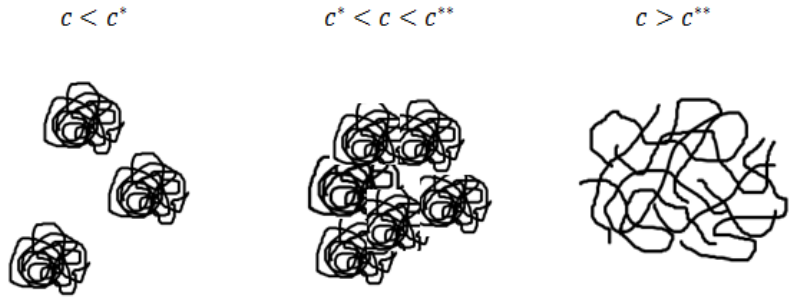


**Figure 2: Behavior of polymers in different concentration ranges (13).**

## 1.3. SOLID DISPERSION

According to previous studies (19), a pharmaceutical solid dispersion is the dispersion of one or more active ingredients in an inert carrier matrix at solid state. More detailed definition says that solid dispersions are largely amorphous mixtures of the active pharmaceutical ingredient (API) and usually polymeric carrier (7). A wide range of processes can be used to prepare amorphous solid dispersion. Among them spray drying and hot melt extrusion may be the most used processes. The choice between these two usually depends on the thermo liability of the drugs. Additionally other methods could be used like melting method, solvent evaporation using a vacuum oven and supercritical anti-solvent method (7). Amorphous state of the drug renders a higher apparent solubility and/or a higher dissolution rate for the drug as compared to crystalline state of the drug. Solid dispersion method is therefore mainly used for oral dosage forms to increase the dissolution rate and consequently improve bioavailability of poorly water soluble drugs by dispersing them into water soluble carriers. Lately some studies also investigate solid dispersion technique using water insoluble, water swellable polymer to develop controlled release dosage form for the poorly water soluble drugs (20).

## 1.4. SPRAY DRYING PROCESS

Spray drying is a process that transforms a feed from a fluid state into a solid state, often in a dried particulate form, by spraying the feed into a hot drying medium (21). It has a wide range of applications in different industries, including the pharmaceutical where it can be used in wide range of fields such as stabilizing biologics, producing inhalable dry powder, producing solid dispersion and micro-encapsulation of bio-actives. The process offers a variety of advantages compared to other technologies used for preparation of solid dispersions. One of the most important advantages is that spray drying could be used for both thermo liable and heat resistant substances, whereas for example melt extrusion is not suitable to prepare solid dispersion from heat sensitive materials. In addition, the characteristics of the particles produced by spray drying can be controlled and particles can be designed for certain purposes. There are also some limitations of the spray drying process. In the production of solid dispersion, using organic solvent, potential residual solvent in the product can be disadvantage as compared to hot melt extrusion. Additionally limited versatility in producing particles or structures with complex morphologies and a burst effect exhibited because of the rapid drug release rates could appear by using spray drying process (21, 22).

There are three major phases involved in spray drying process. At the beginning, the feed is atomized into fine spray in a drying chamber. Depending on the type of energy that is

involved (centrifugal energy, pressure energy, kinetic energy and vibrations), several types of atomization devices are available. The most commonly used atomizer are the rotary disk atomizer and pressurised nozzle, which is suitable for large scale manufacturing of dry products with a large particle size. When finer particles are required either two – fluid nozzle or ultrasonic nozzle is used. Since the size of spray dried particle is largely dependent on the size of the initial droplet size, atomization conditions are considered to be one of the most important parameters to control the final particle size and size distribution (23, 24).

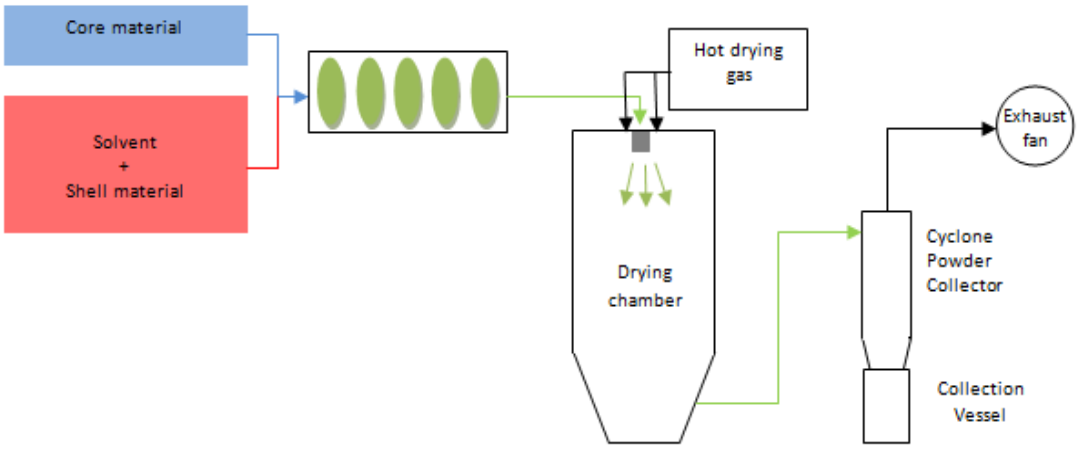


**Figure 3: Scheme of spray drying process (25).**

In the second phase fine spray of the feed is brought into contact with hot drying gas, resulting in the spontaneous evaporation of the solvent contained in the droplets. The feed can be a solution, suspension, emulsion, dispersion and also paste, as the solvent medium either water or organic solvent can be used. Air is typically used as a drying medium in the spray drying process, but when the feed contains organic solvents or when the product should not be in contact with oxygen during the drying an inert gas, usually nitrogen is used. The mixing of the feed and drying gas can be co-current, mixed flow or counter-current. The co-current mixing is most commonly used due to its flexibility and low risk of heat damaging the product. The feed is sprayed in the same direction as the flow of the hot drying gas through the apparatus therefore the droplets come into contact with the hot drying medium when they are the most moist. With an evaporation of the solvent the heat energy of hot gas is carried away, resulting in a reduced thermo-stress on the solute. Mixed-flow dryers are typically equipped with either a fountain nozzle system or a combined spray dryer – fluid bed dryer. In the last, the product is sprayed upwards and only remains in the hot zone for a very short time to eliminate the residual moisture. Due to gravity the product is then pulled into the cooler

zone. Using a fountain nozzle system, larger and thermally stable particles are produced. Spraying via counter-current mode the material is sprayed in the opposite direction of the flow of hot drying gas. During the process the product becomes very hot, therefore this method is suitable only for thermally stable products (19, 23).

The last phase of the spray drying process is the separation of the solid material from the drying gas stream, which is performed using a cyclone and / or bag filter (22). The whole process is schematically presented in figure 3.

**Table II: The interplay between process and formulation parameters (26).**

| dependence / parameter | OUTLET TEMPERATURE | PARTICLE SIZE | FINAL HUMIDITY OF PRODUCT | YIELD |
|---|---|---|---|---|
| ↑ ASPIRATOR RATE | ↑↑ less heat losses based on total inlet of energy | - | ↑↑ lower partial pressure of evaporated water | ↑↑ better separation rate in cyclone |
| ↑ AIR HUMIDITY | ↑ more energy stored in humidity | - | ↑↑ higher partial pressure of drying gas | (↓) more humidity can lead to sticking product |
| ↑ INLET TEMPERATURE | ↑↑↑ direct proportion | - | ↓↓ lower relative humidity in gas | (↑) eventually dryer product prevent sticking |
| ↑ SPRAY GAS FLOW | ↓ more cool gas to be heated up | more energy for fluid dispersion | - | - |
| ↑ FEED RATE | ↓↓ more solvent to be evaporated | (↑) more fluid to disperse | ↑↑ more water leads to higher particle pressure | (↓↑) depends on application |
| SOLVENT INSTEAD OF WATER | ↑↑↑ less heat of energy of solvent | (↓) less surface tension | ↓↓↓ no water in feed leads to very dry product | ↑↑ no hygroscopic behaviour leads to easier drying |
| ↑ CONCENTRATION | ↑↑ less water to be evaporated | ↑↑↑ more remaining product | ↓ less water evaporated, lower partial pressure | ↑ bigger particles lead to higher separation |

Understanding the interplay between process parameters and formulation parameters, presented in the table II, is crucial to achieve a spray dried product with desirable characteristics. Furthermore spray dried particle characteristics are determined by evaporation rate of the solvent and the diffusion rate of solute in the droplets during the evaporation (27).

The typical process parameters in spray drying, which can be considered, include inlet and outlet temperature, atomising gas flow rate (atomisation energy), feed rate, the humidity of drying gas, etc (22, 26). On the other hand formulation parameters to consider are feed composition including both solvent type and the ingredient of solutes, and solid concentration of the feed. In addition, physicochemical properties of the feed such as surface tension of the drying solution, viscosity of the feed influence the spray dried particle characteristics such as size, shape, density and surface chemistry.

### 1.5. SOLID STATE ANALYSIS

Stability of the drug formulations is one of the most important requirements for pharmaceutical development. The physical stability of the drug in solid dispersions can be characterized by various analytical techniques. Due to the complexity of solid state of a drug in the solid dispersion there is no single characterization technique that can gather all the necessary information on solid dispersion. Therefore most of these techniques are used together to complement each other (28).

- **POWDER X-RAY DIFFRACTION** measures diffraction of X-rays in the crystal lattice. The apparatus consist of an X-ray tube with filters giving monochromatic radiation and detector that measures the diffracted beam intensity at different diffraction angles. It is an indispensable tool to characterize and to control the quality of crystalline and amorphous materials (28).
- **THERMAL ANALYSIS TECHNIQUES**

  Differential scanning calorimetry and thermogravimetric analysis, are mostly employed for the characterization of solid state pharmaceuticals. Former measures heat emission and heat absorption as a function of temperature, while TGA measures weight change as a function of temperature (28).
- **FURIER TRANSFORM INFRARED SPECTROSCOPY** gives information about the nature and the extent of interactions between drug molecules and between drug molecules and excipient molecules in solid dispersion (28).
- **RAMAN SPECTROSCOPY** is mainly used as a quantitative method for studying crystalinity and polymorph analysis. Vibrational, rotational, and other low-frequency modes in a system could be observed using Raman spectroscopy (29). It provides us with generally stronger spectra from drug compounds than that generated from most excipients (28).

## 2. AIM

The aim of the project was to study the influence of different solvents, thus intrinsic viscosity on polymer – polyvinyl acetate characteristics, therefore at the beginning rheological study of different polyvinyl acetate solutions was performed.

Furthermore the focus of this study was to study the effect of the conformation of PVAc in the feed in combination with process variables on some quality attributes of spray-dried product, i.e. particle morphology, physical stability of drug in the solid dispersion upon storage as well as the dissolution rate of the given drug - celecoxib.

# 3. MATERIALS AND METHODS

## 3.1. MATERIALS:

***PVAc beads*** (average $M_W$=100kDa), Sigma Aldrich, St. Louis, USA

***CELECOXIB***, Dr. Reddy, Hyderabad, India

Celecoxib is classified in the Biopharmaceustics Classification System as a class II drug (30). For those drugs it is common to have a high permeability and low water solubility (31).

In addition celecoxib is a highly COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). This means that it is involved in aspects of inflammation in which COX-2 products have a role and furthermore it acts as antipyretic and analgesic. It is mostly used to treat osteoarthritis and rheumatoid arthritis (32).

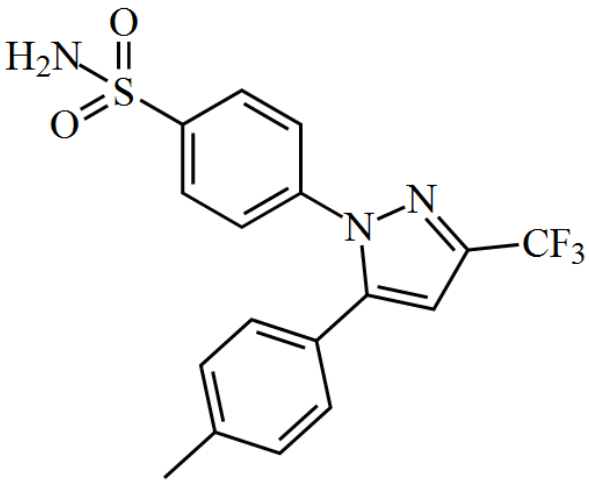


**Figure 4: Chemical structure of celecoxib.**

***SOLVENTS***

- METHANOL, Sigma Aldrich, St. Louis, USA
- ACETONE, Sigma Aldrich, St. Louis, USA
- ETHANOL, Sigma Aldrich, St. Louis, USA

### *BUFFER pH =7,4*

- DISODIUM HYDROGEN PHOSPHATE ($Na_2HPO_4$), Sigma Aldrich, St. Louis, USA
- SODIUM DIHYDROGEN PHOSPHATE ($NaH_2PO_4$), Sigma Aldrich, St. Louis, USA

### *SODIUM LAURYL SULPHATE (SLS)*

It has been used as a surfactant and it was purchased from Sigma Aldrich, St. Louis, USA

## 3.2. APARATURES:

- Cannon-Ubbelohde Semi-Micro Viscosimeter, Cannon Instrument Co., State College, PA, USA;
- Büchi B-290 spray dryer, Büchi Labortechnik AG, Flawil, Switzerland;
- Büchi Inert Loop B-295, Büchi Labortechnik AG, Flawil, Switzerland;
- X-ray powder diffractometer PANalytical X'Pert Pro diffractometer equipped with a PIXcel detector, PANalytical B.V., Almelo, The Netherlands;
- Fourier Transform Infrared spectroscope NICOLET 380, smart orbit with diamond crystal and Omnic software, Thermo scientific Inc; Waltham, USA
- Raman spectroscope Kaiser Optical Systems Inc., Ann Arbor, MI
- TGA 7, Perkin Elmer, Norwalk, CT, controlled by Pyris software.
- JSM-5200 Scanning electron microscope, JEOL, Japan
- E5200 Auto Sputter Coater, Biorad, UK
- Erweka DT-600, a USP type II apparatus, ERWEKA GmbH, Heusenstamm, Germany
- UV-spectroscope Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA
- Analytical balance Mettler Toledo XP26 (DeltaRange Excellence Plus), Mettler Toledo Switzerland
- Analytical balance Mettler AE240, Mettler Toledo Switzerland
- Magnetic stirrer Kika Werke RCT basic, IKA®-Werke GmbH & Co. KG, Staufen, Germany

## 3.3. METHODS:

### *VISCOSIMETRIC MEASUREMENTS OF PVAc, USING DIFFERENT SOLVENTS*

Viscosity was measured by using calibrated Cannon-Ubbelohde Semi-Micro Viscosimeter. The viscosimeter was cleaned with suitable solvents and dried with clean, dry, filtered air flow through the instrument to remove the final traces of solvents. Sample was prepared by diluting known mass of polyvinyl acetate in determined amount of chosen solvent and filtered through the 0,22 micrometer filter. The viscosimeter filled with known volume of the sample was then placed vertically into the constant temperature bath at 25°C. After attaining thermal equilibrium the flow time measurements were performed by a digital stopwatch with uncertainty of 0,01s. The viscosimeter was filled such that the level form point J to point higher than C was achieved. Because of the height difference between point J and point C there is a hydrostatic head or driving pressure to cause the liquid to flow through the capillary or narrow diameter section of the viscosimeter. The efflux time was measured by the time to meniscus pass from mark D to mark F. Each sample was then diluted by addition of measured quantity of solvent directly from pipette into the lower reservoir of the viscosimeter through tube G (figure 5).

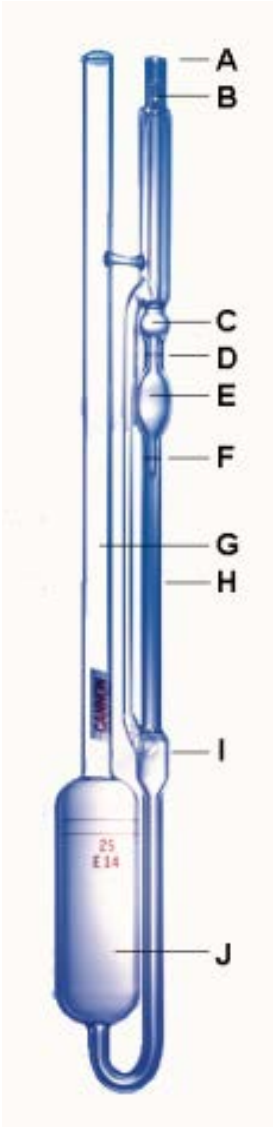


**Figure 5: Scheme of Cannon-Ubbelohde Semi-Micro Viscosimeter (33)**

Afterwards the new sample was carefully mixed according to the *Instructions for the use of the Cannon-Ubbelohde Semi-Micro Viscosimeter* (33) Besides shaking the viscosimeter, slight pressure is applied to the tube B (figure 5) for several times.

The kinematic viscosity of the sample was calculated by multiplying the efflux time by the viscosimeter constant, which was provided by *Certificate of Calibration for used Viscosimeter type form Cannon Instrument Company* (33).

Specific viscosity and relative viscosity for each concentration were then calculated by *eqation 1*. Intrinsic viscosity was further provided by plotting the specific and the relative

viscosities according to Kraemer and Huggins equations to reveal the limitation to the zero concentration, which is value of the intrinsic viscosity.

### *PREPARATION OF AMORPHOUS CELECOXIB, PHYSICAL MIXTURES AND SOLID DISPERSIONS*

Amorphous celecoxib was prepared by dissolving the drug into a sufficient amount of methanol and spray drying (see detailed description of spray drying process below).

Physical mixtures of the drug and polymer were prepared by mixing accurately weighed amounts of drug and polymer. Since we used beads of PVAc in our project, we needed to grind the beads to get particles with diameter smaller than 350µm. Both compounds were sieved trough sieves of 350 µm before mixing.

Solid dispersions of celecoxib and PVAc, in different ratios, were prepared by spray drying. The required amount of the drug and polymer was dissolved either in methanol or in methanol-acetone 1:5 ratio and if necessary, filtered before spray drying (see detailed description of spray drying process below).

### *SPRAY DRYING*

The spray drying process was performed with a Büchi B-290 spray dryer (figure 6b) and Büchi Inert Loop B-295 (figure 6a) (Büchi Labortechnik AG, Flawil, Switzerland). Nitrogen as atomising gas was used in a co-current mode. Spray-dried particles were separated from the drying air by a standard cyclone and manually transferred to glass vials immediately after production. All solutions of a pure PVAc were spray dried with 60°C inlet temperature, 95% aspirator rate, 3mL/min feed rate and 439 L/h air spray flow rate. The outlet temperature varied from 38°C to 44°C. Solutions which contained polymer and drug were spray dried at 60°C of inlet temperature, 95% aspirator rate, 3mL/min feed rate and 439 L/h air spray flow rate. The outlet temperature was kept at 43±2°C. Spray dried product was further put into a glass vial with lid wrapped with ParaFilm and stored with silic gel in desiccators or in at oven at 40°C.



**Figure 6: a) Büchi Inert Loop B-295; b) Büchi B-290 spray dryer (personal archive)**

## *STABILITY STUDY*

In order to investigate the effect of storage time on the re-crystallization behaviour of amorphous celecoxib in the solid dispersion all samples were analyzed immediately after the preparation and then stored in an oven at 40°C prior to further analysis. X-ray powder diffraction, Fourier transform infrared spectroscopy and Raman spectroscopy were used to define the presence of crystalline drug content.

- *X-RAY POWDER DIFFRACTION (XRPD)*

Power X-ray diffractometry were obtained using PANalytical X'Pert Pro diffractometer equipped with a PIXcel detector (PANalytical B.V., Almelo, The Netherlands). A continuous 2θ scan was performed in a range of 2,017°–35,000° using a Cu Kα radiation (λ=1.54187 Å). The Kβ radiation was eliminated by a nickel filter. The voltage and current applied were 45 kV and 40mA, respectively. Each measurement was done with a step size of 0.026°2θ and at a speed of 0.067°/s. Sample spinning was employed during measurements to avoid preferred orientation effects. Data were collected using X'Pert data collector and were analyzed with X'Pert Highscore plus (both from PANalaytical B.V., Almelo, The Netherlands).

- *FURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)*

Samples were analysed using a NICOLET 380 (Thermo scientific), smart orbit with diamond crystal and Omnic software. Spectra were recorded from 4000 $cm^{-1}$ to 525 $cm^{-1}$. For each spectrum, 64 scans were performed at a resolution of 2 $cm^{-1}$.

- *RAMAN*

The Raman spectroscopy were obtain using a wide angle (Phat) probe (Kaiser Optical Systems Inc., Ann Arbor, MI) with a spot size of 3 mm. Pure drug, physical mixtures and spray dried products spectra were collected using a 4 s exposure time and 2 accumulations. A total of 8 s was used to obtain each spectrum.

## *THERMO GRAVIMETRIC ANALYSIS (TGA)*

The residual moisture content of the samples was investigated directly after spray-drying by using a TGA 7 (Perkin Elmer, Norwalk, CT), controlled by Pyris software. Powder samples between 1,3 and 6,8 mg were loaded in a flame-cleaned platinum sample pan and heated from 25 to 200°C at a rate of 10°C/min.

### *SCANNING ELECTRON MICROSCOPY (SEM)*

Particle size and morphology of the samples were checked using a JSM-5200 scanning electron microscope (JEOL, Japan). Samples were mounted on aluminum stubs with double adhesive carbon tape and sputter coated with gold at 20mA for 120s in argon atmosphere prior to microscopy (E5200 Auto Sputter Coater, Biorad, UK)

### *DISSOLUTION STUDY*

Dissolution rates of celecoxib and solid dispersions were studied using Erweka DT-600, a USP type II dissolution test apparatus. Amorphous celecoxib sample (10 mg) and all solid dispersion samples (each 20 mg sample of solid dispersions, should contain 10 mg of the celecoxib) were placed in a dissolution vessel containing 500ml of 0,01M phosphate buffer (pH 6.8) and 1,5 % surfactant, sodium lauryl sulphate (SLS), maintained at 37°C and stirred at 50 rpm. Dissolved samples were collected at the specified time intervals and replaced with an equivalent amount of fresh dissolution medium at 37°C. The vessel was covered for the duration of the test.

- BUFFER SOLUTION was prepared by mixing proper amounts of 0,1 M $Na_2HPO_4$ and 0,1 M $NaH_2PO_4$ and diluting it with distilled water to obtain 0,01 M buffer. For 100mL of phosphate buffer (pH = 6,8) 28,01mL of $Na_2HPO_4$ x $2H_2O$ and 71,99mL of $NaH_2PO_4$ x $2H_2O$ were used.

- UV SPECTROSCOPY was used to quantify the amount of the drug dissolved (Evolution 300, Thermo Fisher Scientific, Waltham, MA, USA). UV spectrum of celecoxib was evaluated in the range of 200-400 nm. Due to the highest molar absorptivity of celecoxib at the wavelength of 253 nm and the high selectivity of this wavelength regarding solvent in the samples the wavelength of 253 nm was selected for detection of drug amount. If necessary, samples were filtered before the analysis trough 0,45 µm filter. Absorption spectra of the sample solutions were measured against the reference solution using 1.0 cm light-path length cuvettes. As the reference pure solvent was used. The spectrum for each sample was collected at room temperature in duplicate, the averaged values were reported. The drug content in the unknown samples was calculated based on the absorbance values from the standard curve, which was previously prepared from the absorbance values of known standard solutions, as described below.

- STANDARD CURVE DETERMINATION

Standard solutions with known concentrations were prepared with dilution of the stock solution. As a solvent phosphate buffer (pH=6,8) was used. As described before the wavelength of 253 nm was selected for detection. From the absorption spectra achieved with standard solutions we draw the standard curve and calculated equation of the curve and $R^2$.

# 4. RESULTS AND DISCUSSION

## 4.1. VISCOSITY:

The viscometric study of the project was focused on three solvents, acetone, methanol and ethanol and their mixtures, in which, according to *Polymer Data Handbook* (34), PVAc is soluble.

The flow times of solutions of polyvinyl acetate in different solvents and with various concentrations of polymer were measured. From these data, specific and relative viscosities were calculated. The calculated values of both are listed in the table III. Furthermore, intrinsic viscosity was determined according to Huggins and Kraemer equations. In the former the intrinsic viscosity of the polymer is obtained by extrapolation of reduced viscosity to zero concentration of the Polyvinyl acetate (figures 7, 8), whereas according to alternative Kraemer equation the intrinsic viscosity is obtained by extrapolation of $\ln\frac{(\eta_{sp}+1)}{c}$ to zero concentration of the polymer (figures 7, 8). Both values of intrinsic viscosities, obtained either by Huggins or Kraemer are listed in the table below (table III). Measurements were preformed in triplicate and average values are presented in the table below (table III).

**Table III: Results of viscosity measurements of polyvinyl acetate in different solvents.**

| ***PVAc in Acetone, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY (mm²/s)* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
|---|---|---|---|---|---|---|
| Acetone | $t_0$ = 108,25 | 0,385 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0,0245 | 363,45 | 1,29 | 2,36 | 1,21 | 54,0 | 55,6 |
| 0,0196 | 292,17 | 1,04 | 1,70 | 0,992 | | |
| 0,0163 | 252,07 | 0,897 | 1,33 | 0,845 | | |
| 0,0140 | 226,60 | 0,806 | 1,09 | 0,738 | | |
| 0,0122 | 209,42 | 0,745 | 0,934 | 0,660 | | |
| 0,00980 | 182,49 | 0,649 | 0,685 | 0,522 | | |

| ***PVAc in Methanol, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
|---|---|---|---|---|---|---|
| Methanol | $t_0$ = 194,33 | 0,692 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0,0161 | 354,7066667 | 1,26 | 0,825 | 0,602 | 38,1 | 39,6 |
| 0,0129 | 317,1666667 | 1,13 | 0,632 | 0,490 | | |
| 0,0108 | 292,5133333 | 1,04 | 0,505 | 0,409 | | |
| 0,00717 | 258,2233333 | 0,919 | 0,329 | 0,284 | | |
| 0,00461 | 231,78 | 0,825 | 0,193 | 0,176 | | |
| ***PVAc in Methanol : Acetone 1:2, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *Native logarithm of RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
| Methanol : Acetone 1:2 | $t_0$ = 119,90 | 0,427 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0,0214 | 337,72 | 1,20 | 1,82 | 1,04 | 62,1 | 60,5 |
| 0,0171 | 290,52 | 1,03 | 1,42 | 0,885 | | |
| 0,0134 | 246,98 | 0,879 | 1,06 | 0,723 | | |
| 0,00954 | 203,28 | 0,723 | 0,695 | 0,528 | | |
| 0,00613 | 169,71 | 0,604 | 0,415 | 0,347 | | |
| ***PVAc in Methanol : Acetone 1:4, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
| Methanol : Acetone 1:4 | $t_0$ = 113,44 | 0,40373296 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0,0202 | 309,79 | 1,10 | 1,73 | 1,00 | 58,1 | 59,4 |
| 0,0162 | 262,12 | 0,933 | 1,31 | 0,838 | | |
| 0,0126 | 225,69 | 0,803 | 0,990 | 0,688 | | |
| 0,00897 | 185,18 | 0,659 | 0,632 | 0,490 | | |
| 0,00577 | 156,15 | 0,556 | 0,376 | 0,320 | | |

| ***PVAc in Methanol : Acetone 1:5, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
|---|---|---|---|---|---|---|
| Methanol : Acetone 1:5 | $t_0$ = 112,41 | 0,400 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0,0197 | 300,18 | 1,07 | 1,67 | 0,982 | 65,0 | 62,7 |
| 0,0158 | 259,17 | 0,922 | 1,31 | 0,835 | | |
| 0,0131 | 229,90 | 0,818 | 1,05 | 0,715 | | |
| 0,00985 | 196,24 | 0,698 | 0,746 | 0,557 | | |
| 0,00716 | 170,16 | 0,606 | 0,514 | 0,415 | | |
| ***PVAc in Methanol : Acetone 4:1, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
| Methanol : Acetone 4:1 | $t_0$ = 167,62 | 0,597 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0.0199 | 388,77 | 1,38 | 1,32 | 0,841 | 47,7 | 48.0 |
| 0,0159 | 335,77 | 1,20 | 1,00 | 0,695 | | |
| 0,0124 | 290,72 | 1,03 | 0,734 | 0,551 | | |
| 0,00884 | 250,41 | 0,891 | 0,494 | 0,401 | | |
| 0,00568 | 218,20 | 0,777 | 0,302 | 0,264 | | |
| 0,00331 | 195,93 | 0,697 | 0,169 | 0,156 | | |
| ***PVAc in Ethanol : Acetone 1:4, T=25°C*** | *AVERAGE TIME (s)* | *AVERAGE KINEMATIC VISCOSITY* | *SPECIFIC VISCOSITY* | *RELATIVE VISCOSITY* | *INTRINSIC VISCOSITY by Kraemer [η] (mL/g)* | *INTRINSIC VISCOSITY by Huggins [η] (mL/g),* |
| Ethanol : Acetone 1:4 | $t_0$ = 122,53 | 0,436 | | | | |
| Concentration of PVAc, [c] (g/mL) | t | | | | | |
| 0.0199 | 329,37 | 1,17 | 1,69 | 0,988 | 65,4 | 63,2 |
| 0.0159 | 282,17 | 1,00 | 1,303 | 0,834 | | |
| 0.0125 | 240,91 | 0,857 | 0,966 | 0,676 | | |
| 0.00886 | 204,00 | 0,726 | 0,665 | 0,510 | | |
| 0.00569 | 171,61 | 0,611 | 0,400 | 0,337 | | |

[mL/g] = how many mL of solvent is occupied by 1g of polymer

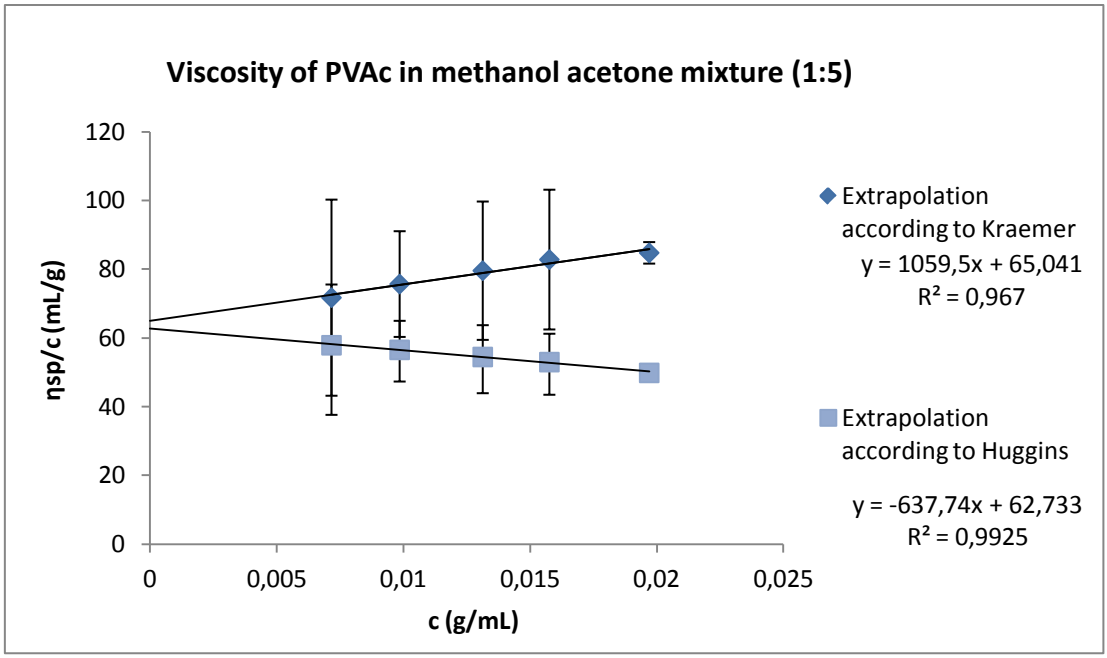


**Figure 7: Extrapolation according to Huggins and Kraemer equations for polyvinyl acetate in methanol-acetone 1:5 micture.**

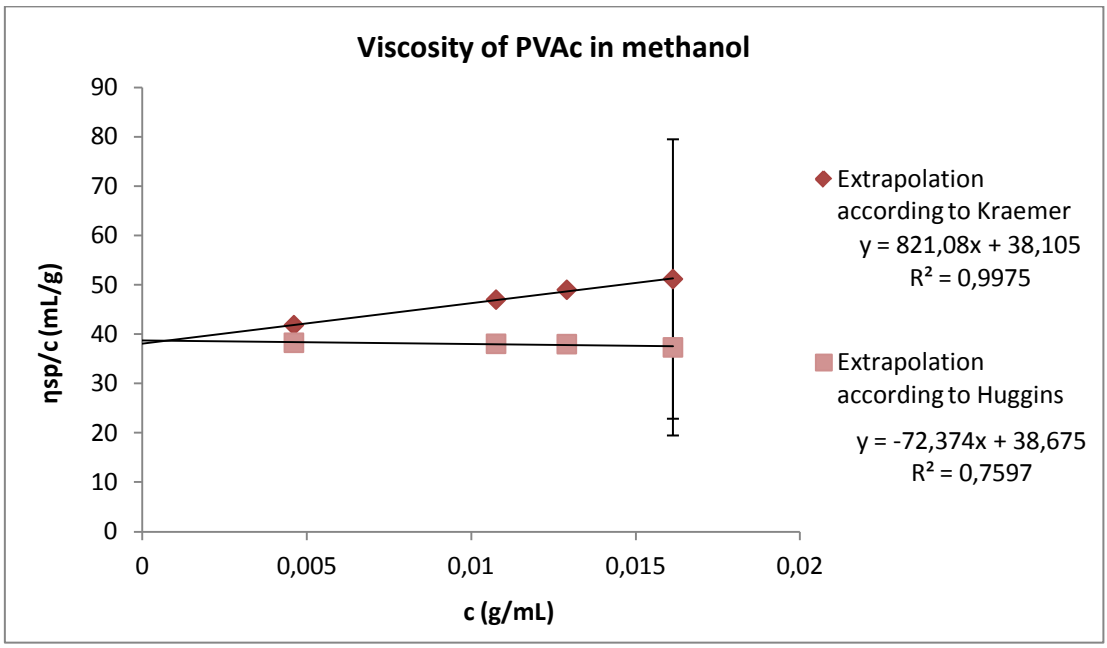


**Figure 8: Extrapolation according to Huggins and Kraemer equations for polyvinyl acetate in methanol.**

Intrinsic viscosities obtained from Huggins and Kraemer equations were found comparable (table III and figures 7, 8). Furthermore from the figures 7 and 8, which show plots of Kraemer and Huggins equation for two samples using polymer-solvent pairs, it can be seen

that there is a linear relationship between both, $\eta_{sp}/c$ and concentration of polymer and $\ln \frac{(\eta_{sp}+1)}{c}$ and concentration polymer in the whole concentration range studied.

From results listed above it can be concluded that the intrinsic viscosity values in methanol-acetone mixtures of PVAc increase with an increase in volume fraction of acetone in solvent mixture, indicating that methanol-acetone 1:5 mixture is the best solvent for PVAc and pure methanol is the worst. It was also found that intrinsic viscosity values in the ethanol-acetone 1:4 mixture are higher than those in the acetone alone, indicating that addition of ethanol increase the solubility and therefore intrinsic viscosity of Polyvinyl acetate in acetone. Molecules in the dissolved, molten, amorphous, and glassy states of macromolecules exist as random coils. For dilute solutions, it is known, that the volume associated with each polymer coil contains large mass of solvent around one polymer molecule. Hydrodynamic volume of those coils therefore depends upon the polymer molecular weight and its thermodynamic interactions with the solvent.

In the current study polymer – solvent interactions in methanol-acetone and ethanol-acetone mixtures are stronger than in pure methanol, which lead to higher solvation swelling of the polymer chains in the solutions and thus increases the intrinsic viscosity of the polymer solution. Those findings are also in correlation with Hansen and Hildebrand solubility parameters, listed in the table IV. Theoretical Polyvinyl acetate solubility parameter, calculated in the theoretical background, is 18,50 $MPa^{1/2}$. From previous findings (14) it is known that polymers display maximum swelling in solvents with polarity similar to their polymeric backbone. That was verified by Burton et al., who applied Hildebrand parameter for correlating swelling of different types of polymeric material. Those findings also suggest that the polymer would swell the most and will have the greatest intrinsic viscosity in the solvent which has the closest value of solubility parameter to the value of polymer. In our study we revealed that solubility parameter of Methanol differ more from the solubility parameter of Polyvinyl acetate than Acetone solubility parameter (table IV). Therefore it is understandable that the mixtures with higher ratio of Acetone provide higher solvation of the polyvinyl acetate thus higher value of intrinsic viscosity.

The Hildebrand and Hansen solubility parameters of the solvents used throughout our project are listed in the table IV.

**Table IV: Hildebrand and Hansen solubility parameters for the solvents used in our study.**

| SOLVENT | Hildebrand solubility parameter [δ] ($MPa^{1/2}$) | Hansen solubility parameter ($MPa^{1/2}$) | | | |
|---|---|---|---|---|---|
| | | $\delta_T$ | $\delta_D$ | $\delta_P$ | $\delta_H$ |
| acetone | 19,70 | 20,7 | 15,5 | 10,4 | 7,0 |
| methanol | 29,0 | 29,6 | 15,1 | 12,3 | 22,3 |
| ethanol | 25,7 | 26,5 | 15,8 | 8,8 | 19,4 |
| Methanol:Acetone=1:2 | 22,8 | 23,7 | 15,4 | 11,0 | 12,1 |
| Methanol:Acetone=1:4 | 21,6 | 22,5 | 15,4 | 10,8 | 10,0 |
| Methanol:Acetone=1:5 | 21,3 | 22,2 | 15,4 | 10,7 | 9,6 |
| Methanol:Acetone=4:1 | 27,1 | 27,7 | 15,2 | 11,9 | 19,2 |
| Ethanol:Acetone=1:4 | 20,9 | 21,9 | 15,6 | 10,1 | 9,5 |

Values of the pure solvents are from Barton, 1975, whereas the values of the blended solvents are calculated from values of the pure solvents by eqution: $\bar{\delta} = \sum_i \phi_i \, \delta_i$

Based on findings about correlation between intrinsic viscosity values and polymer swelling, three solvents were chosen which according to the viscosity studies has different effect on polyvinyl acetate for further studies. Those were methanol-acetone 1:5 mixture, which is according to viscosity studies a good solvent, methanol which is a poor solvent for polyvinyl acetate and methanol-acetone 4:1 mixture which has the intrinsic viscosity between the values of intrinsic viscosities of polymer solutions with methanol and methanol-acetone 1:5 mixture. Additionally, it can be assumed that polyvinyl acetate is in extended form, dominant polymer - solvent interactions, when dissolved in the methanol-acetone 1:5, less extended is in methanol-acetone 4:1 mixture and in methanol there are unfavourable interactions between solvent and polymer thus polyvinyl acetate is in folded conformation.

## 4.2. SPRAY DRYING PROCESS

As mentioned before pure polymer was dissolved in three different solvents, methanol, methanol-acetone 1:5 mixture and methanol-acetone 4:1 mixture. Additionally three different concentration ranges were defined, c*, below c* and above c*. Feed solutions at c*

concentration of the polymer had the same viscosity therefore comparison between properties of spray dried particles from different solvents at the same viscosity of the feed solution could be revealed. Furthermore, spray drying of the solutions with the concentration of polymer below c* were conducted to study differences of spray dried products from the diluted polymer solutions, where polymer molecules are not in continuous contact with each other. In addition spray drying of polymer solutions with a concentration above c* were conducted to compare the particles produced from the concentrated feed solutions, where polymer chains are in continuous contact with each other.

The calculation of the c* for given polymer – solvent pairs were calculated according to the equation 12 as it is shown below.

$$c^*(PVAc\ in\ MeOH) = \frac{1}{[\eta]} = \frac{1}{38{,}10\frac{mL}{g}} = 0{,}026 g/mL$$

$$c^*(PVAc\ in\ MeOH - Acetone\ 1{:}\ 5) = \frac{1}{[\eta]} = \frac{1}{65{,}04\frac{mL}{g}} = 0{,}015 g/mL$$

$$c^*(PVAc\ in\ MeOH - Acetone\ 4{:}\ 1) = \frac{1}{[\eta]} = \frac{1}{47{,}73\frac{mL}{g}} = 0{,}021 g/mL$$

### *4.2.1. SPRAY DRYING OF PURE POLYMER SOLUTIONS*

In the table V, yields and residual moisture of the spray dried products are listed.

**Table V: Spray drying temperatures, yield and residual moisture values of pure polymer spray dried products.**

| MeOH | | |
|---|---|---|
| PVAc [c] (%) | Yield (%) | Residual moisture (%) |
| 0,5 | 46 | 0,063 |
| 2,6 (c*) | 61 | 0,074 |
| MeOH:Acetone (1:5) | | |
| PVAc [c] (%) | Yield (%) | Residual moisture (%) |
| 0,5 | 33 | 0,441 |
| 0,8 | 61 | 0,679 |
| 1,5 (c*) | 73 | 0,614 |
| 3,0 | 54 | 0,761 |
| MeOH:Acetone (4:1) | | |
| PVAc [c] (%) | Yield (%) | Residual moisture (%) |
| 0,5 | 39 | 0,419 |
| 2,1 (c*) | 69 | 0,980 |

As seen from table V the yields of spray dried powder varied from 33% to 73%. The yield of the spray dried powder decreased with a decrease in the concentration of PVAc in the solution. It could be due to finer particles were produced with a decrease in the polymer concentration (owing to low viscosity). It is known with the cut-off diameter of particle with the cyclone used in this study is around 1 µm. The particles lower than 1µm could go directly from the separation cyclone to the filter and losses.

The residual moistures of the products have been provided by thermo gravimetric analysis. All of the samples had residual moisture below 1% therefore the post drying process was not needed. Additionally with an increase in the concentration of the polymer in the feed solution a slight increase in the moisture content was obtained. The final moisture level of the spray drying product is mostly determined by the possibility of polymer molecules to interact with the given solvent. In correlation with favourable solvent-polymer interactions it was also in our study revealed (table V) that the better the solvent is the higher the value of moisture is as it can be seen also from the figure below (figure 9).

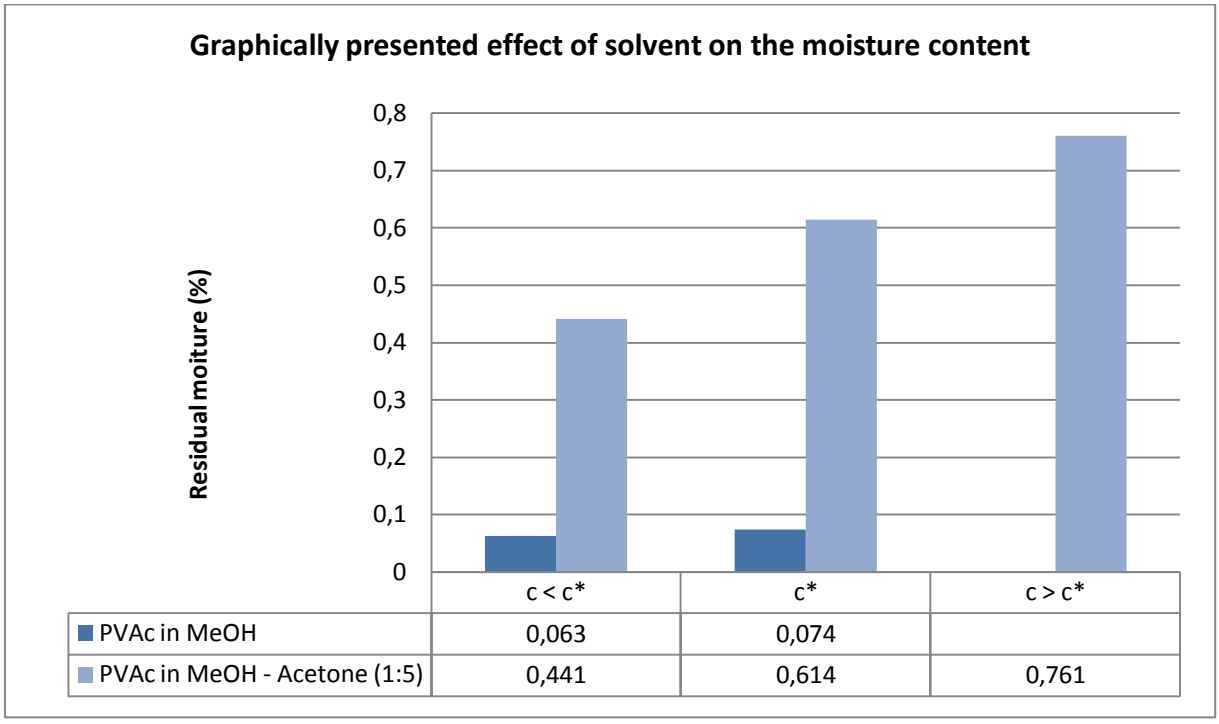


**Figure 9:Final moisture level in different polymer samples.**

Outlet temperature is often used to reflect the highest temperature of the solid particles that can reach in the spray drying process. It is a resulting temperature of the heat and mass balance in the drying cylinder. Outlet temperature in the spray drying can be regulated by adjusting different spray drying process parameters – inlet temperature, aspirator flow rate, peristaltic pump setting and concentration of the material being sprayed. In our study inlet temperature 60°C was carefully determined. Namely this temperature is close to the boiling points of the solvents used, it is below the melting point of the polymer and most importantly we achieve the outlet temperatures from 38°C to 44°C which is still not well above the $T_g$ of the polyvinyl acetate and our amorphous polymer still did not became rubbery and sticky.

### *4.2.2. SCANNING ELECTRON MICROSCOPY (SEM) OF SPRAY DRIED PURE POLYMER PARTICLES*

The morphology of the spray dried particles was obtained using scanning electron microscope. As the SEM pictures (figures 10, 11) of particles spray dried from different solutions of PVAc revealed, there are major differences in shape between particles spray dried from methanol and those spray dried from methanol-acetone mixture whereas the size of the particles is similar for all the spray dried particles.

A key factor that determines the size of spray dried particle is atomization therefore the selection of atomizer should be carefully determined. Two–fluid nozzle was chosen, which is a commonly used atomizer to produce fine particles. Since the atomizing flow rate was kept the same for all feed solutions, the size of particles can be expected to be similar for all spray dried products. From the SEM pictures (figures 10, 11) it is revealed that the particles are in the same size range, but more detailed particle size analysis such as laser diffraction should be performed for more precise evaluation of the size similarity.

The shape and morphology of the particles produced via spray drying are mostly determined by the rate of droplets evaporation and the diffusion of the solutes in the feed solution upon drying. The droplet to particle conversion is processed when droplets, generated from the atomizer enter the chamber and getting contact with the hot drying gas. With an evaporation of the solvent, the solute is condensed spontaneously. During drying the atomised spray undergoes changes such as expansion, collapsing or disintegration which can lead either to porous irregularly shaped particles, hollow or spherical particles.

As shown Figure 10 and 11 the particles spray dried from poor solvent (methanol) are collapsed, while the particles spray dried from good solvent (methanol-acetone 1:5 mixture) are spherical. However, the polymer concentration does not have a significant effect on the particle morphology and size. Except for 3% (figure 10) PVAc sample spray dried from methanol-acetone 1:5 mixture, where too high concentration/viscosity could be a reason for incompletely formed spherical particles.

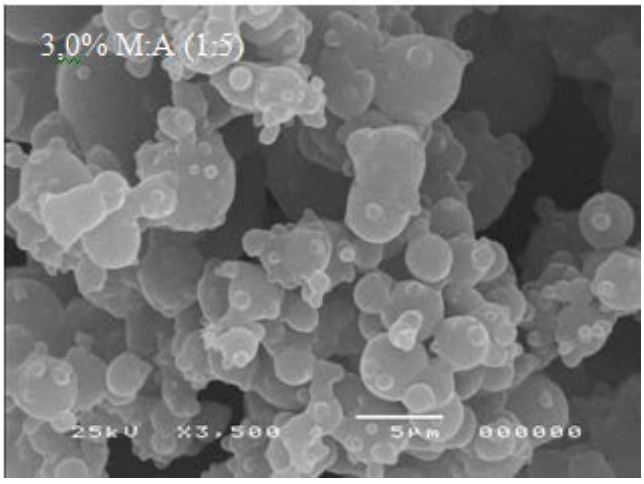


**Figure 10: SEM picture of the 3% PVAc in methanol-acetone 1:5 mixture.**

Since there were no differences in spray drying parameters while spray drying different solutions made from different solvents, which could affect differently the shape of the spray dried particles. The reasons for differently shaped particles could be mostly due to different evaporation rate of given solvents. Furthermore to explain the variations in particles shape, the knowledge about differences between the inlet temperature and boiling points of solvents is needed. Boiling point of methanol is 65°C, while boiling point of acetone is 57°C. Due to higher amount of polymer – polymer interactions the polymer precipitated fast and formed a shell when methanol is used alone. However the texture of the shell was not strong enough to keep the spherical shape of the particle. Whereas when good solvent used, polymer – solvent interactions are favourable and polymer precipitate slower. In the methanol-acetone 1:5 mixture, acetone will evaporate faster than methanol, due to its lower boiling point, thus the ratio of the solvents will be changed during the process. There was some shrinking of polymer shell upon drying. Hence the shell might become a bit thicker that produced from pure methanol. A cross section of the particles could be considered to test this speculation.

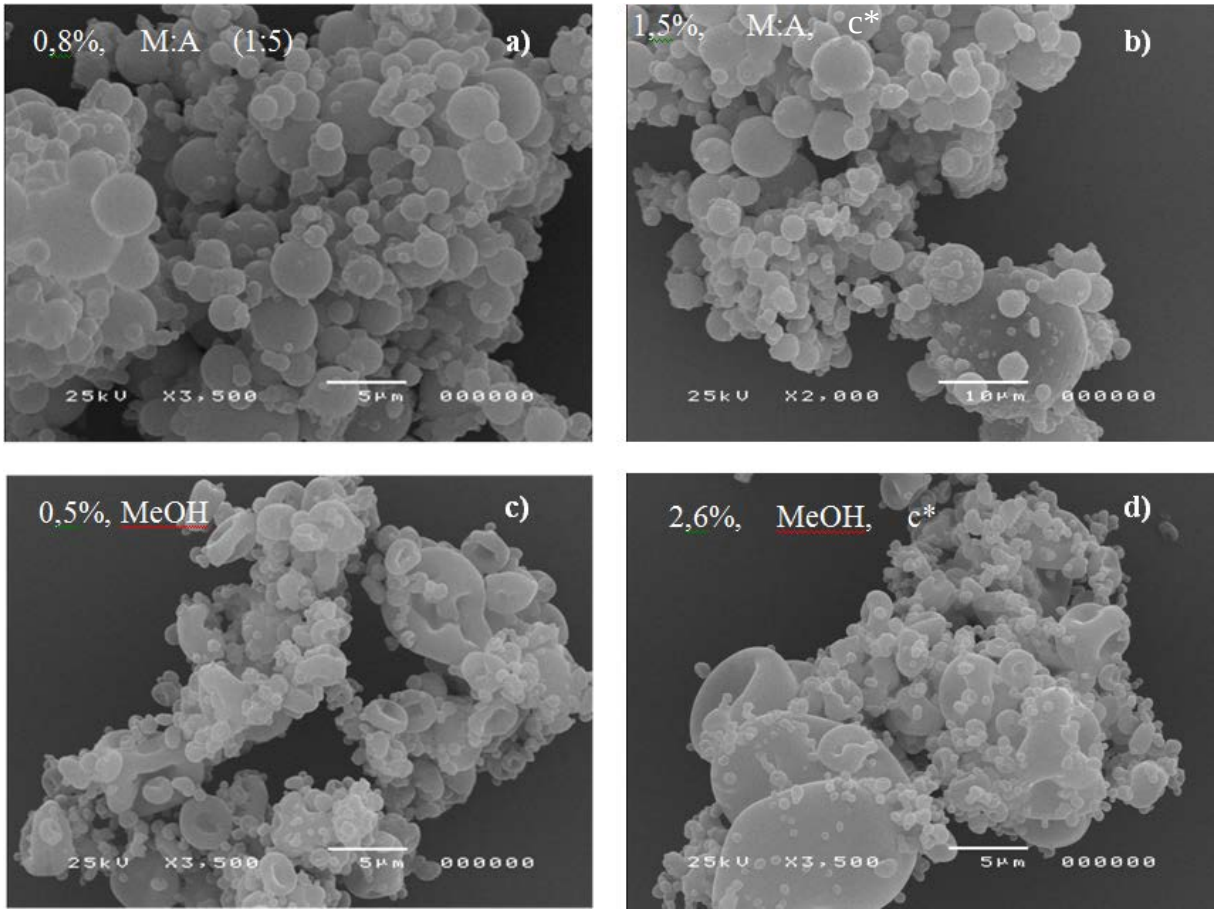


**Figure 11: a) SEM picture of the 0,8% PVAc in methanol-acetone 1:5 mixture; b) SEM picture of the 1,5% PVAc in methanol-acetone 1:5 mixture; c) SEM picture of the 0,5% PVAc in methanol; d) SEM picture of the 2,6% PVAc in methanol.**

### *4.2.3. SPRAY DRYING OF FEED CONTAINING POLYMER AND ACTIVE SUBSTANCE*

After revealing the rheological properties and investigating the morphology of spray dried particles of polyvinyl acetate alone, the effect of given polymer, solvents and spray drying process parameters on the solid dispersion particles containing active pharmaceutical ingredient – celecoxib was investigated. The main objective of this study was to study how different solvent compositions will influence solid state stability of the model drug and the dissolution rate of drug from the produced solid dispersion. Firstly the same amount of Celecoxib and Polyvinyl acetate were dissolved in two of the given solvents, i.e. methanol and methanol-acetone 1:5 mixture. The spray drying process parameters were the same as used in the previous study, i.e. aspiration rate was 95%, atomizing gas flow rate was 439 L/h, and feed rate was 3 mL/min. Inlet temperature was kept at 60°C and the values of outlet temperatures varied from 41°C - 45°C.

As it was already defined in the introduction the term solid dispersion refers to a group of solid products consisting of at least two different components, generally a polymeric matrix and a drug. The matrix can be either crystalline or amorphous (35). In our case solid dispersion was made from hydrophobic matrix and hydrophobic drug.

Spray drying of the solutions with the concentration of polymer above c* was again challengeable because of the fibres that appeared especially in the solution with concentrations of polyvinyl acetate and celecoxib above c* in methanol indicating that there were non-dissolved polymer present. In term of the correlation between lower concentrations and lower yield we have not proved it with the samples containing polyvinyl acetate together with celecoxib.

As it can be seen from the table VI, yields of the solid dispersion products were higher than for the pure polymers (table V), the only exception is again 3% solid dispersion spray dried from methanol-acetone mixture where the outlet temperature unpredictably raised and it was probably too high compared to PVAc's glass transition temperature which is on average around 35°C.

The residual moisture of the products spray dried from poor solvent (methanol) revealed by thermo gravimetric analysis was close to half of percentage, while the values of residual moisture in solid dispersion spray dried from good solvent (methanol-acetone mixture) were a bit higher but still close to 1%. Again the post drying process was not required.

As we have already revealed with the results of polymer alone a higher concentration of the polymer in the feed solution leads to the slight increase of the moisture content. This was obtained also for the polymer-drug 1:1 mixtures. Furthermore study revealed (table VI) that the in better solvent higher value of moisture content is achieved.

**Table VI: Spray drying temperatures, yield and residual moisture values of solid dispersion products.**

| MeOH | | | |
|---|---|---|---|
| PVAc content (%) | PVAc:API | Yield (%) | Residual moisture (%) |
| 0,6 | 1:1 | 80 | 0,374 |
| 2,6 (c*) | 1:1 | 68 | 0,559 |
| MeOH:Acetone (1:5) | | | |
| PVAc content (%) | PVAc:API | Yield (%) | Residual moisture (%) |
| 0,6 | 1:1 | 50 | 1,054 |
| 1,5 (c*) | 1:1 | 66 | 1,076 |
| 3,0 | 1:1 | 19 | 1,203 |

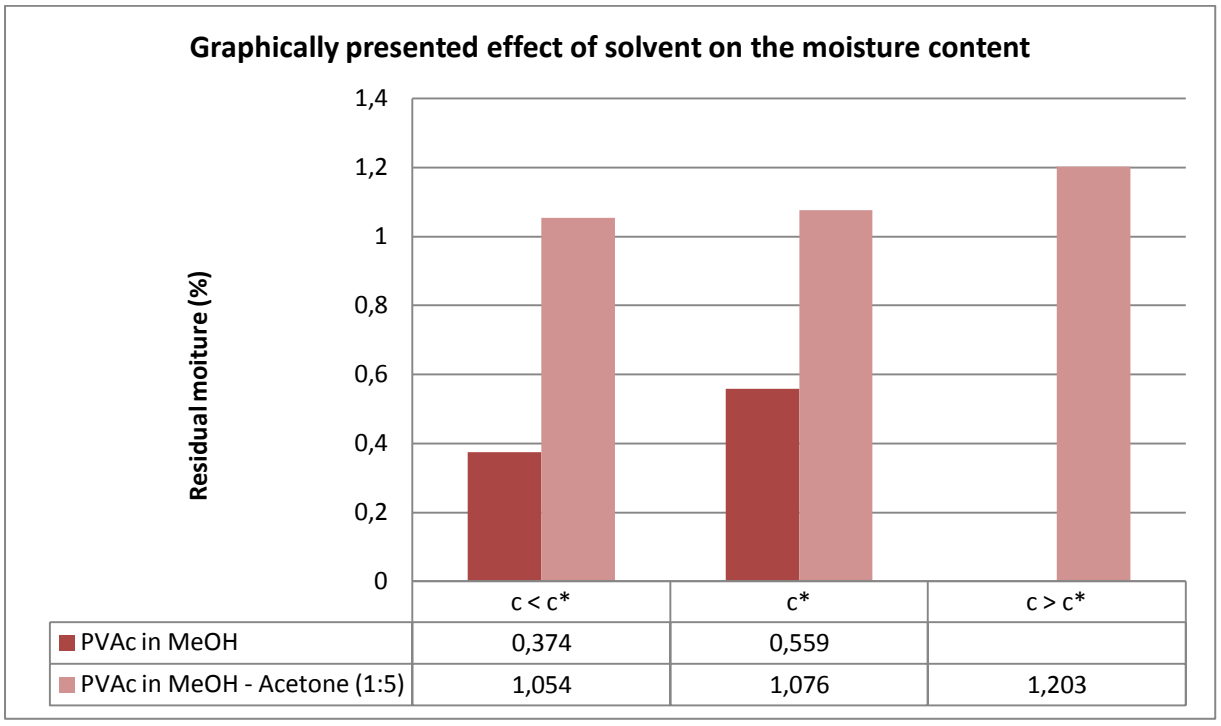


**Figure 12: Final moisture level in different soild dispersion samples.**

Additionally from the TGA spectra it was obtained that solid dispersion particles was produces by spray drying, while only one peak of weight loss could be determined. As the

example TGA spectra of solid dispersion spray dried from 0,6% PVAc/0,6% celecoxib dissolved in methanol-acetone 1:5 mixture is shown in the figure 13.

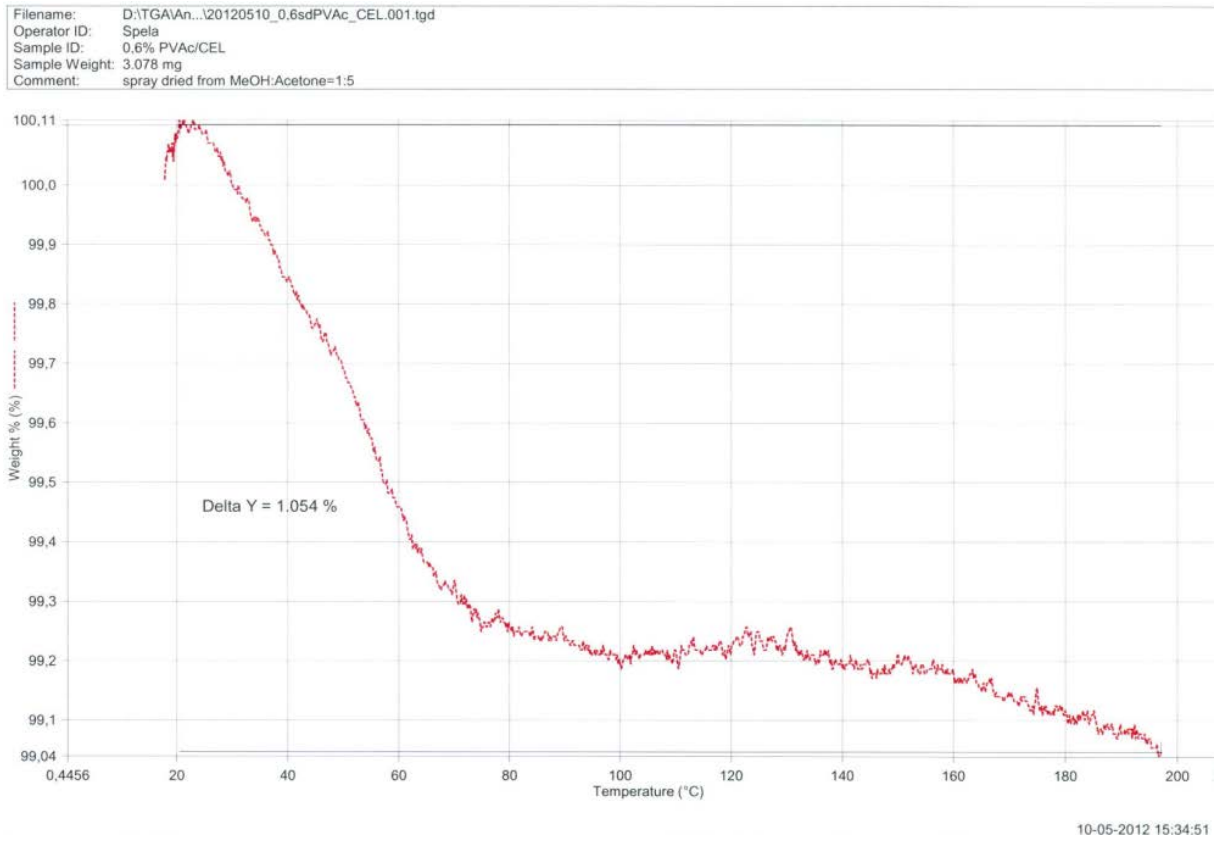


**Figure 13: TGA spectra of solid dispersion spray dried from 1,5% PVAc/1,5% celecoxib dissolved in methanol-acetone 1:5 mixture.**

### *4.2.4. SCANNING ELECTRON MICROSCOPY (SEM) OF SPRAY DRIED SOLID DISPERSION PARTICLES*

After producing solid dispersion by spray drying the morphology of the spray dried particles was again obtained using scanning electron microscope. The SEM pictures (figure 14) of solid dispersion particles revealed that particles spray dried from methanol-acetone 1:5 mixture are spherical, regardless to the addition of the drug and concentration of the solution from which the solid dispersion was made. Particles, which were prepared by spray drying of feed solution consisting of polymer, drug and methanol, turned out a bit differently as they did when polymer was spray dried alone, while not only the polymer but also the precipitation of the drug influenced on the morphology of the particles. Particles did not collapse when the celecoxib was present, but there are still some dents in their surface.

That difference could appear due to the lowering the polymer – polymer interactions because of newly appeared polymer-drug interactions which leads to less compact conformation and furthermore the linking of the polymer after evaporation is not present as much as it is when the polymer is used alone. Additionally the effect of difference in boiling points of methanol and methanol-acetone 1:5 mixture again renders particles spherical when fast evaporation is present when feed solution contains methanol-acetone 1:5 mixture. But when using methanol different evaporation rate of the solvent does not have such significant effect on solid dispersion particles compared to the pure polymer particles.

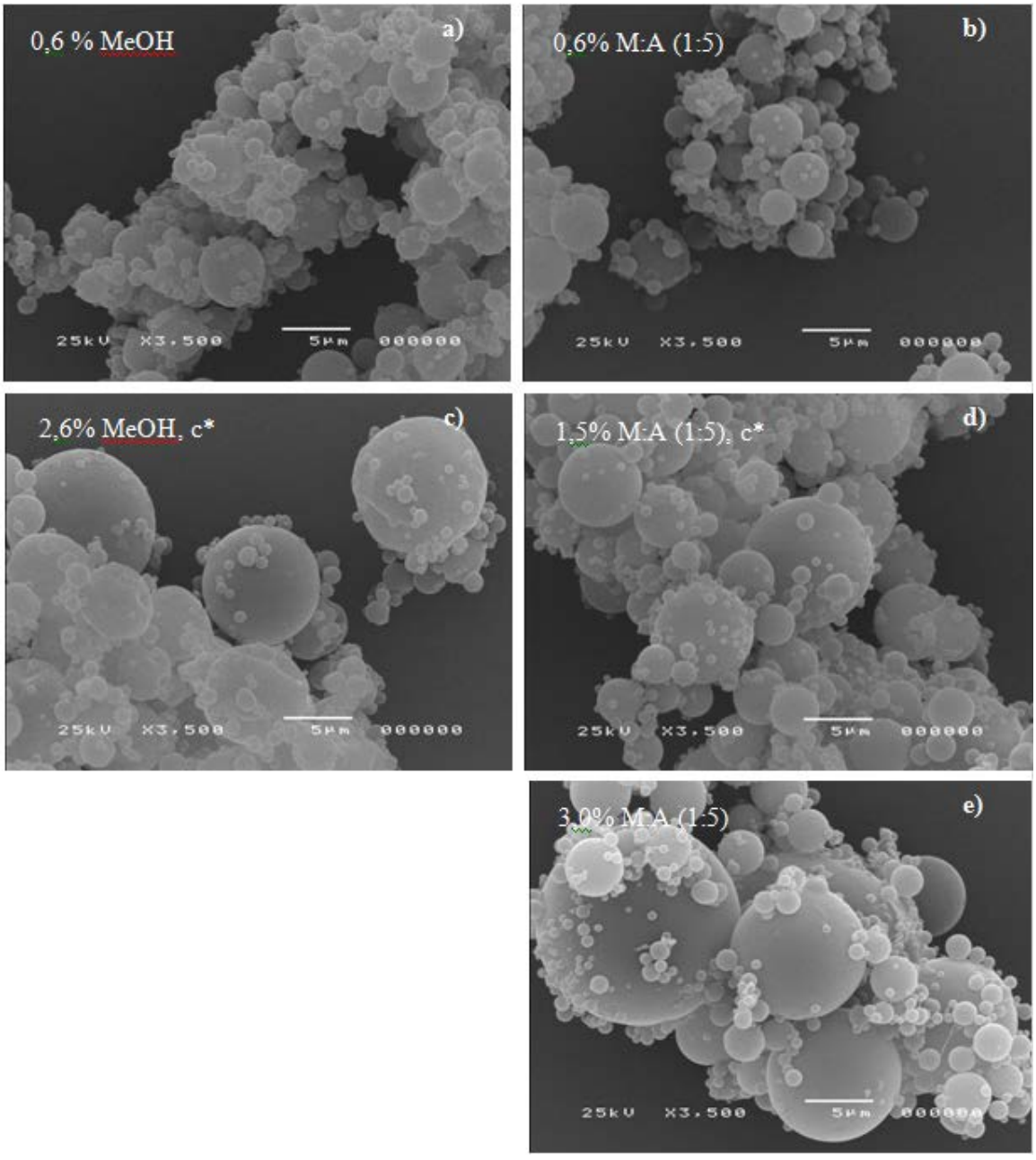


**Figure 14: a) SEM picture of the 0,6% PVAc and 0,6% celecoxib in methanol; b) SEM picture of the 0,6% PVAc and 0,6% celecoxib in methanol-acetone 1:5 mixture; c) SEM picture of the 2,6% PVAc and 2,6% celecoxib in methanol; d) SEM picture of the 1,5% PVAc and 1,5% celecoxib in methanol-acetone 1:5; e) SEM picture of the 3,0% PVAc and 3,0% celecoxib in methanol-acetone 1:5.**

## 4.3. SOLID STATE ANALYSIS

Several analytical techniques that are commonly used to study solid state stability of amorphous drug were included in our project, i.e. X-ray power diffraction, Fourier transform infrared spectroscopy and Raman spectroscopy.

XRPD is one of the most sensitive and foolproof methods for solid state characterization as the results are obtained directly from the molecular arrangements of the crystalline material. (36)

As it can be seen from the diffractogram below, (figure 15) the most characteristics peaks in the XRPD pattern of crystalline celecoxib are positioned at 2θ angles from 10° to 30°. The physical mixture of crystalline CEL and PVAc (ratio 1:1) show the characteristic peaks with lower intensities, which is due to dilution of the drug content with PVAc. Characteristic peaks are completely absent in amorphous celecoxib and pure PVAc patterns.

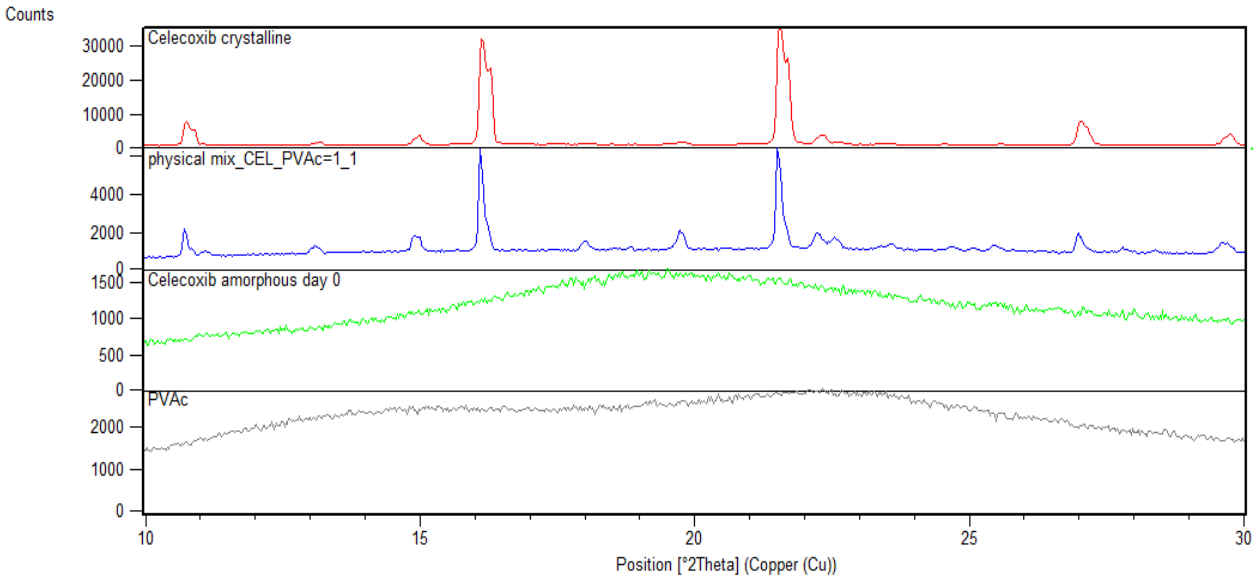


**Figure 15: XRPD patterns of crystalline CEL, amorphous CEL, physical mixture and PVAc.**

Regarding the XRPD diffractogram in figure 16, there is no sign of recrystallization in our amorphous CEL - PVAc solid dispersion samples for 35 days. Stability could be attributed to the capturing drug into polymer and hydrogen bonding interactions between amorphous CEL and PVAc. Explanation of different effect on stability of solid dispersion will be described in the following paragraphs.

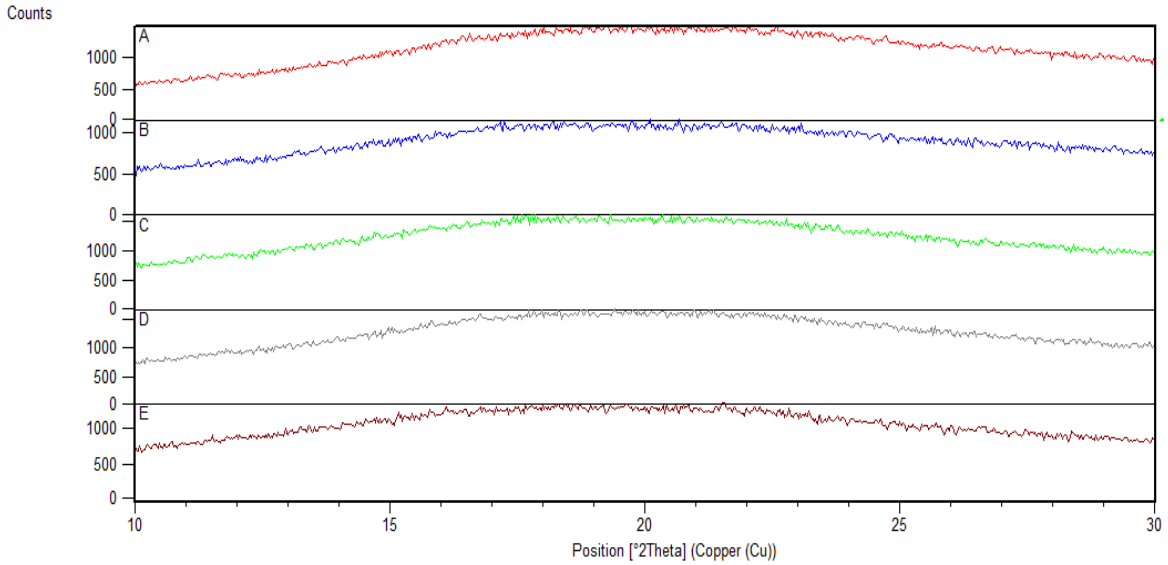


**Figure 16: XRPD patterns of soli dispersions after 35 days. A- 0,6% CEL : 0,6% PVAc (M:A), B- 0,6% CEL : 0,6% PVAc (M), C- 1,5% CEL : 1,5% PVAc (M:A), D- 2,6% CEL : 2,6% PVAc (M), E- 3,0% CEL : 3,0% PVAc (M:A).**

The comparative assessment of FTIR spectra (figure 17) revealed C-F stretching vibration band of crystalline CEL at 1228 $cm^{-1}$ to shift to a higher wave number of 1235 $cm^{-1}$ for amorphous CEL. Further the S=O asymmetric stretching vibration band observed at 1345 $cm^{-1}$ for crystalline CEL shifts to a broader hump at lower wave number of 1335 $cm^{-1}$ for amorphous CEL. Another major difference was evident for the N-H stretching vibration of $–SO_2NH_2$ group. Sharp doublet which shifted from 3328 $cm^{-1}$ and 3223 $cm^{-1}$ in crystalline CEL to 3351 $cm^{-1}$ and 3261 $cm^{-1}$ in amorphous CEL also becomes much broader for amorphous CEL.

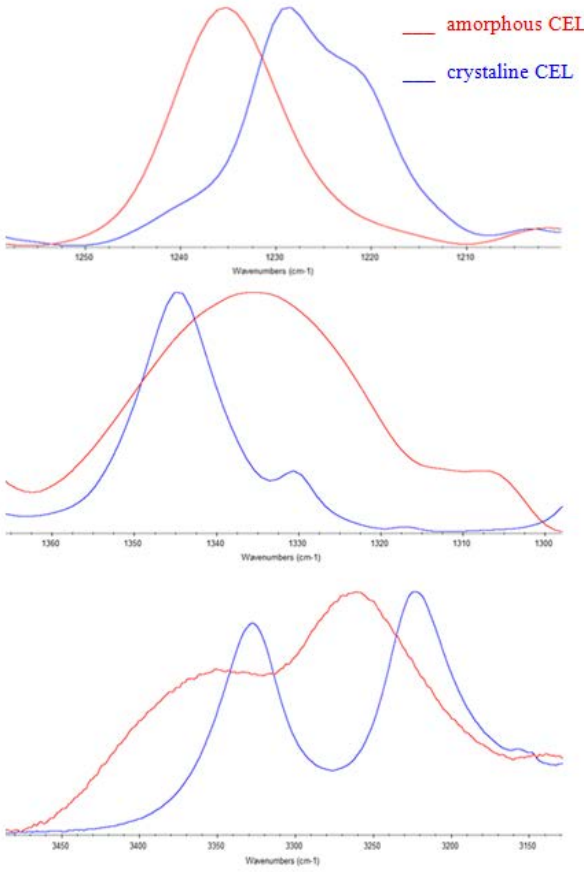


**Figure 17: FTIR characteristic peaks for CEL molecule.**

As it was previously described by *Piyush Gopta et. al.* (37) These broadness and shifts in vibration frequencies indicated greater strength of average H-bonding for N-H as well as C-F in the ordered phase and for S=O in the disordered phase. This could be explained based on the differences in participating atoms in the H-bond formation.

Both of N-H groups of the same molecule in the crystalline celecoxib form were found to be involved in bifurcated H-bonding with the S=O group, 2-N of pyrazole ring and C-F group of different celecoxib molecules, whereas, in the amorphous form, only one N-H group per celecoxib molecule H-bonds and the other is free. This greater extent of H-bonding of the N-H group results in lower N-H vibration wave number in crystalline celecoxib despite a weaker H-bond that in the amorphous form. Further S=O group was associated with ring formation in the amorphous form. The delocalization of electrons over the ring helped stabilizing this particular conformation, strengthening the interaction in the amorphous form, reflected as shift of the S=O stretching vibration band to a lower wave number as compared with the crystalline form where S=O group is involved in chain formation. C-F group showed shift at a higher wave number for amorphous celecoxib where it interacts only with single H atom, while in the crystalline form single F atom participate in bifurcated H-bonding with two different atoms.

To further understand H-bonding between CEL and PVAc in the solid dispersions we also need to reveal at least one characteristic peak for our polymer. Therefore in the figure 22 you can see C=O characteristic peak of PVAc at 1728 $cm^{-1}$. Which will be important for further explanation (table VII) of H-bonding between polymer and drug.

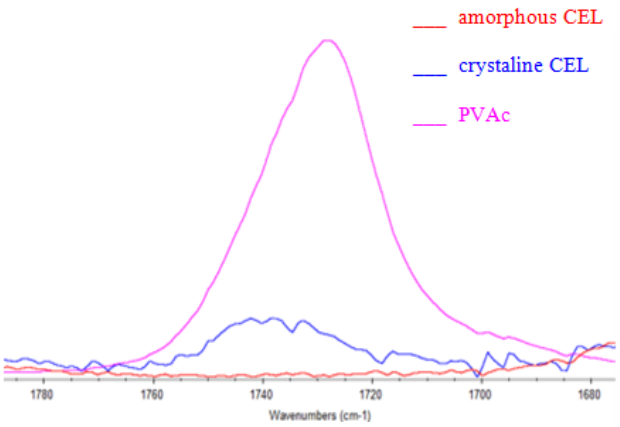


**Figure 18: FTIR characteristic peak for PVAc.**

Raman observations are in good agreement with data obtained from FTIR spectroscopy, again providing evidence of shifting and broadening the peaks of amorphous CEL. From the spectrum below (figure 19, table VII) we can see that the peaks which are attributed to N-H group, 1613.6 $cm^{-1}$, 1598.4 $cm^{-1}$, and the symmetrical S=O, 1160.7 $cm^{-1}$, and C-F, 1228.8 $cm^{-1}$ vibration peaks of crystalline CEL are shifted, broadened and differently shaped for the amorphous form. Therefore N-H peaks of amorphous form are shifted to higher wave numbers at 1618.1 $cm^{-1}$ and 1600.0 $cm^{-1}$. Further also C-F peak is shifted to a higher wave number 1239.0 $cm^{-1}$, whereas is S=O stretching vibration band shifted to lower wave number, 1157.4 $cm^{-1}$, which again provide evidence of a strengthening of intermolecular hydrogen bonding interactions formed by S=O groups and a weakening in such interactions formed by C-F and N-H groups in the amorphous form of celecoxib.

In Raman spectrum C=O characteristic peak of PVAc can be seen at 1730.4 $cm^{-1}$.

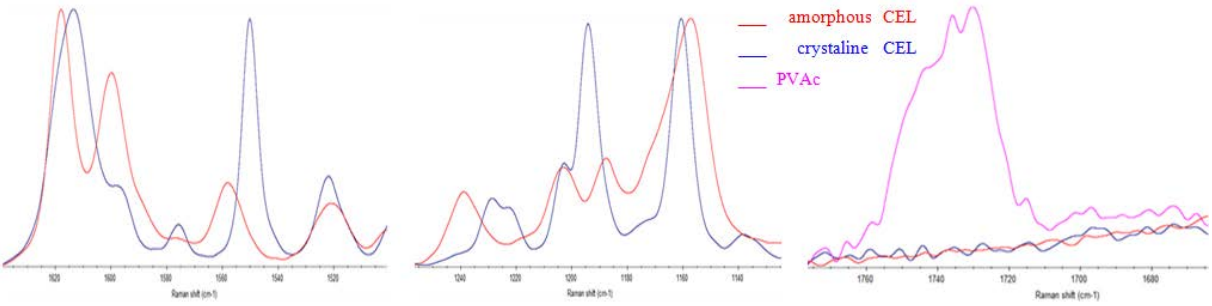


**Figure 19: Raman characteristic peaks for amorphous CEL, crystalline CEL and PVAc.**

**Table VII: Solid dispersions shifts of characteristic peaks.**

| | | FTIR | | | Raman |
|---|---|---|---|---|---|
| | | N-H ($cm^{-1}$) | | C=O ($cm^{-1}$) | S=O ($cm^{-1}$) |
| crystalline CEL | | 3328 | 3323 | | 1160.7 |
| amorphous CEL | | 3351 | 3261 | | 1157.4 |
| PVAc | | | | 1728 | |
| ***drug:polymer*** | ***solvent*** | | | | |
| 0.6% :0.6% | methanol | 3339 | 3255 | 1732 | 1163.2 |
| 0.6% :0.6% | methanol:acetone (1:5) | 3339 | 3257 | 1733 | 1162.5 |
| 1.5% :1.5% | methanol:acetone (1:5) | 3334 | 3254 | 1732 | 1163.2 |
| 2.6% :2.6% | methanol | 3333 | 3240 | 1732 | 1163.2 |
| 3.0% : 3.0% | methanol:acetone (1:5) | 3341 | 3256 | 1733 | 1163.2 |

Raman and FTIR spectra of solid dispersions remain the same even after 35 days, while in pure amorphous CEL recrystallization occurs already after four days. That confirms some previous findings that amorphous drug is more stable in solid dispersion as when we have pure amorphous drug (5-8). There are two main reasons for that. PVAc is a macromolecule which could capture drug molecule into the polymeric coil and shielding from the outside environment. Besides capturing also H-bonds between drug and polymer can form while preparing solid dispersion.

In our case C=O group of PVAc molecule is an electron acceptor while CEL have S=O and C-F as electron acceptors and N-H group as an electron donor functional group. From the FTIR spectra of our solid dispersions (figure 20) it can be seen that there are some peak shifts to a lower energetic state of N-H group of CEL and also some small changes in peak for C=O

group of PVAc (table VII), which suggest that there could be some hydrogen interactions between the drug and polymer. That can additionally make amorphous CEL more stable.

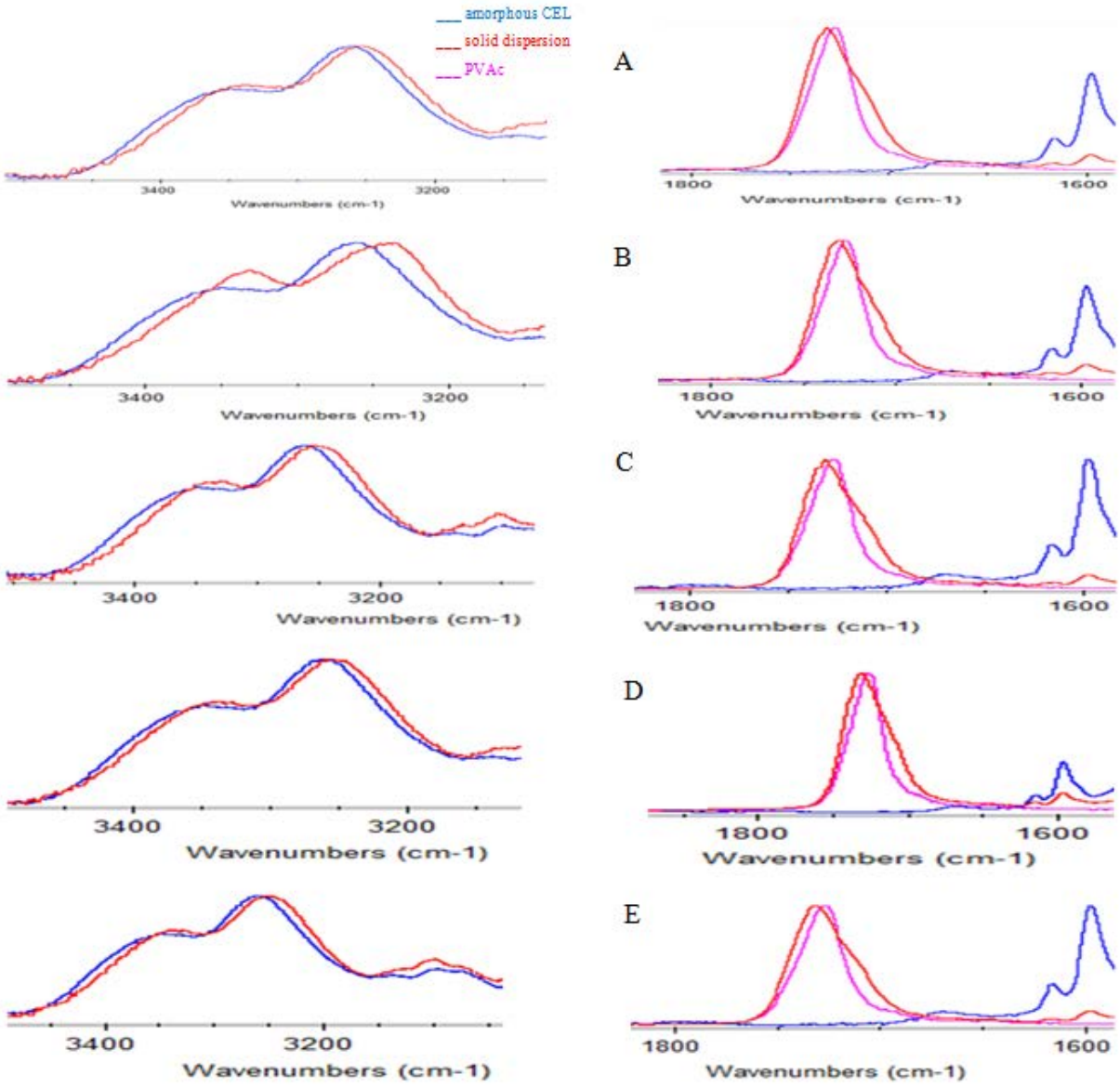


**Figure 20: Changes between FTIR spectra of different solid dispersions samples and amorphous CEL. A- 3%CEL:3%PVAc (M:A); B- 2,6%CEL:2,6%PVAc (MeOH); C- 1,5%CEL:1,5%PVAc (M:A); D- 0,6%CEL:0,6%PVAc (M:A); E-0,6%CEL:0,6%PVAc (MeOH).**

Raman spectra confirm those findings, because the peak of S=O group of CEL molecule is shifted to higher wave numbers (figure 21, table VII) which indicates strengthening of the S=O bond and weakening of secondary interactions in which it can be involved.

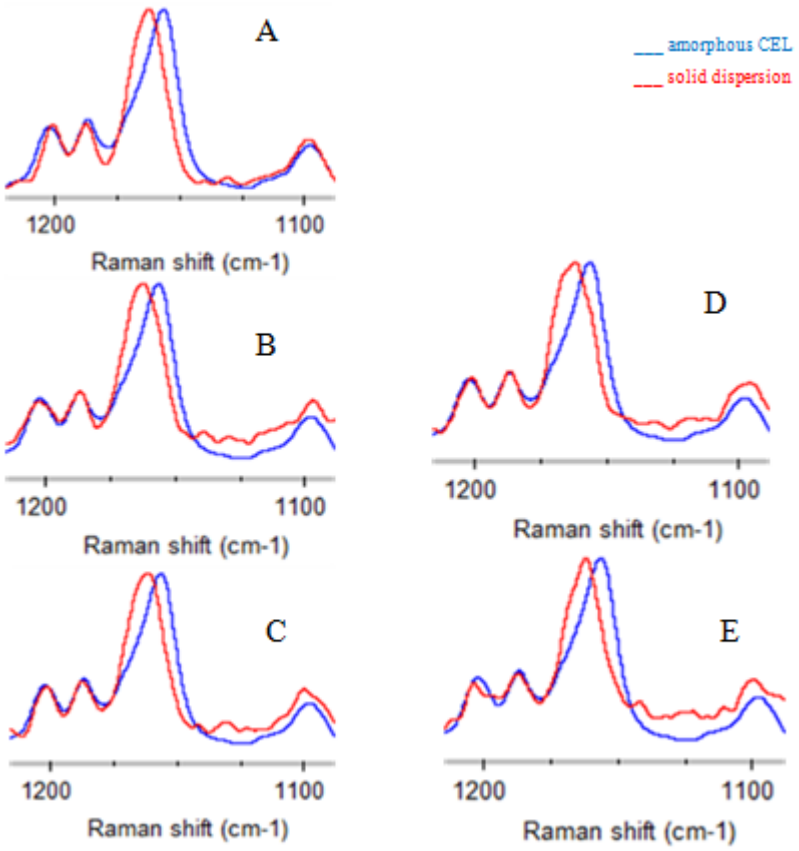


**Figure 21: Raman spectra shifts of S=O peak in solid dispersions. A-3%CEL:3%PVAc (M:A), B- 1,5%CEL:1,5%PVAc (M:A), C-0,6%CEL:0,6%PVAc (M:A), D-2,6%CEL:2,6%PVAc (MeOH), E-0,6%CEL:0,6%PVAc (MeOH).**

From those findings it can be concluded that carbonyl group of PVAc can act as a stronger proton acceptor than sulphonyl functional group of CEL. Differences can be attributed to loss of CEL-CEL H-bonding interactions involving S=O and N-H group of celecoxib and formation of cohesive CEL-PVAc H-bonds involving C=O of PVAc and N-H of CEL, where C=O would act as a proton acceptor and N-H as a proton donor.

## 4.4. DISSOLUTION STUDY

The dissolution profiles of crystalline CEL and solid dispersions are shown in the Figure 23. Dissolution tests were made as the procedure described in the European Pharmacopoeia, 7th edition.

At the beginning the standard curve (figure 22) was prepared. Stock solution prepared by dissolution of polymer-drug mixture into phosphate buffer (pH=6,8) was diluted to prepare five standard solutions. Samples were further detected at the previously determined wavelength 253 nm.

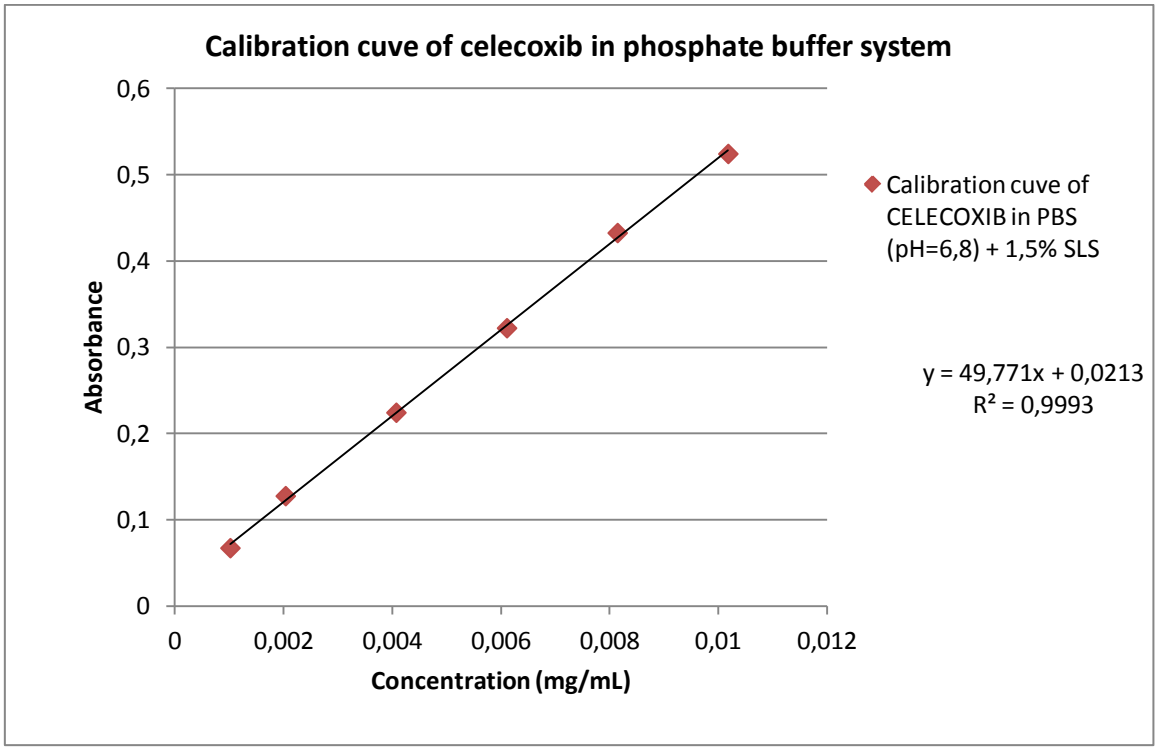


**Figure 22: Standard curve of celecoxib dissolved in phosphate buffer (pH=6,8).**

According to the standard curve (figure 22) we further determined the concentrations of the samples collected from the dissolution test at given times.

Since the polyvinyl acetate is in water in-soluble polymer and celecoxib is poorly soluble polymer we predicted that our solid dispersions would have slowed dissolution profile then the celecoxib itself. The results confirmed that all solid dispersions made from CEL and PVAc have lower dissolution rate than crystalline drug by itself (figure 23). However some differences between different solvents used to make solid dispersion appeared.

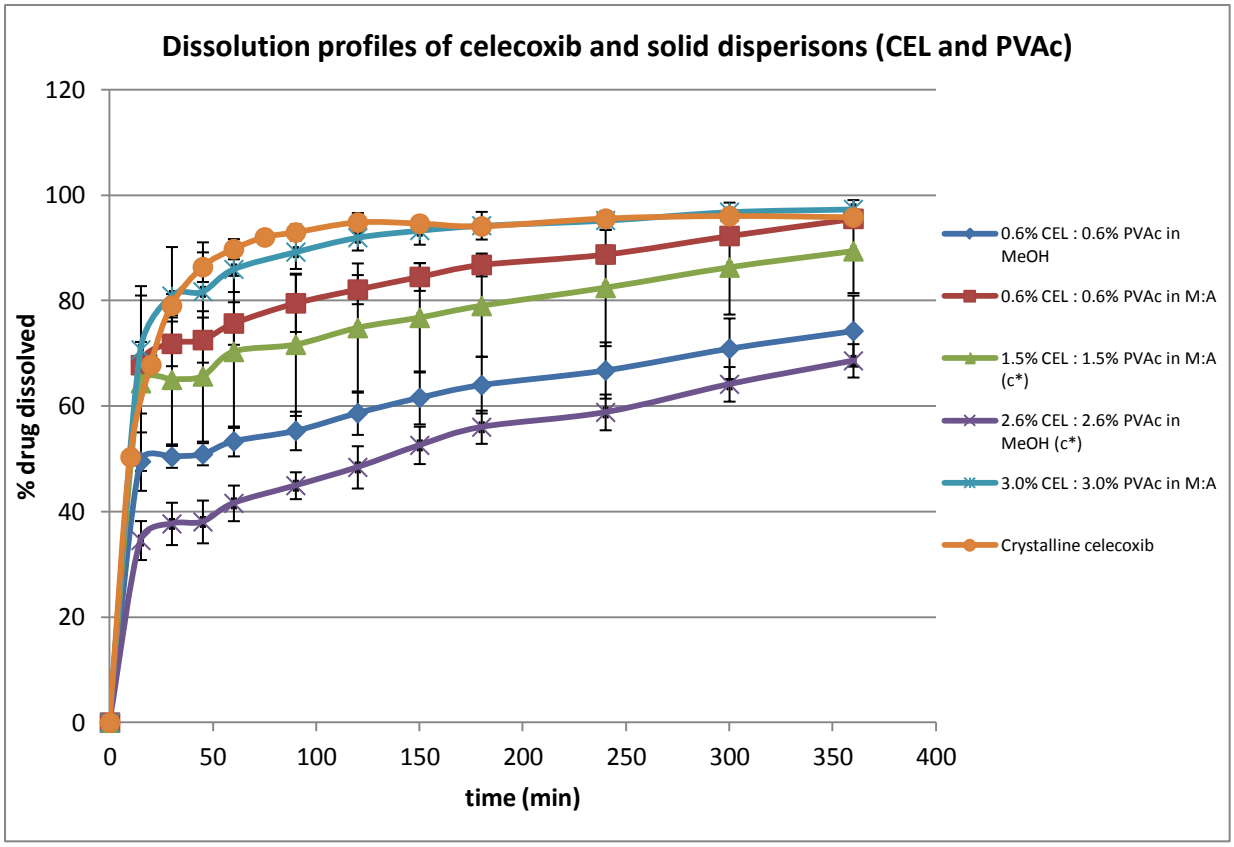


**Figure 23: Dissolution rates of crystalline CEL and solid dispersions of CEL and PVAc.**

From the dissolution profile of solid dispersions prepared from methanol (a poor solvent), seems that percentage of released drug after 360 minutes decreased the most. It could be also seen that the longest time for 50% of the drug to be released ($t_{1/2}$) is gained using methanol solvent for preparation of feed solution and when the concentration of the polymer is the highest. This could be due to strong polymer-polymer interactions in methanol, which lead to more compact, folded form of the polymer and thus possibility that drug is captured in those folded coils. In correlation with the last mentioned finding it can be concluded that the higher the polymer concentration is the slower is the dissolution rate of the drug, because more polymer-polymer interactions could appear.

Similar results were revealed for the samples spray dried from the feed solution which was prepared from the good solvent, methanol-acetone 1:5 mixture. However there was an obvious difference in the dissolution rate from particles prepared with methanol as a solvent. The amount of released drug is closer to 100% after 360 minutes; additionally the 50% of the drug was dissolved already after 10 minutes, regardless of the polymer concentration used. This is understandable while the polymer is in more extended form and therefore the drug is less captured in the polymer thus it can dissolve faster.

The solid dispersion prepared from methanol-acetone 1:5 mixture below and at c*, could be revealed that higher concentration of polymer lead to lower dissolution rate. The difference for solid dispersion prepared with 3% PVAc 3% celecoxib feed solution could be obtained because the outlet temperature of spray drying process was higher than in other samples, thus it was more than 10°C higher compared to $T_g$ of polymer, which could lead to unbalanced drug:polymer ratio in solid dispersion.

It is previously known that the shape of the particles prepared by spray drying could have an important effect on the dissolution profiles. While all solid dispersion particles are almost spherical, just few particles spray dried from methanol have some dents in the surface, we expect that shape of our particles should not have important impact on dissolution rate.

The results obtained from the plot (figure 23) proved that even though the drug was molecularly dispersed as an amorphous form in the solid dispersion the retarding effect of the polymer on the release celecoxib is the dominating factor the dissolution test.

# 5. CONCLUSION

This study focused on the behaviour of the water non-soluble polymer polyvinyl acetate. Revealing its rheological properties in different solvents was fundamental for further investigations. With knowledge that the lowest intrinsic viscosity of polyvinyl acetate is according to the solvents used in methanol and it increase with the increasing volume fraction of acetone. In correlation with the revealed intrinsic viscosity values, the polymer-solvent interactions are more favourable in further used methanol-acetone 1:5 mixture than in methanol. Those findings are in correlation with Hansen and Hildebrand solubility parameters, thus polymer swell the most viscosity in the solvent which has the closest value of solubility parameter to the value of polymer. Therefore in methanol the polymer is more folded and in methanol-acetone 1:5 it is in more extended conformation. Those predictions were confirmed by additional studies of morphology, stability and dissolution profile of spray dried particles of polyvinyl acetone alone or solid dispersion particles prepared from polyvinyl acetate and celecoxib.

Furthermore the findings from this study suggested that the conformational structure (speculated from rheological properties of the polymer in different solvent compositions) of the polymer in the different solvent composition could influence the morphology of the spray-dried particles and dissolution rate of the drug from the solid dispersion.

Scanning electron microscopy pictures revealed that the shape of particles spray dried from methanol-acetone 1:5 mixture was mostly spherical regardless of the concentration and substances used (pure polymer or polymer and drug). Whereas particles spray dried from methanol are collapsed when spray drying only polymer and spherical with some dents when making solid dispersion of polyvinyl acetate and celecoxib. As it was described in the Results and discussions part those differences are most likely present due to different evaporation rate of solvents.

The stability of amorphous celecoxib is improved when a solid dispersion with PVAc is made. As it could be seen from the results pure amorphous drug start to recrystalize after 4 days, while according to our XRPD data, in solid dispersions celecoxib stayed amorphous even after 35 days. Improved stability can be due to polymer – drug hydrogen interactions, which were obtained from FTIR and Raman spectroscopy and also due to polymer capturing the drug into its structure. Furthermore the obtained differences in solid state stability might appear because the drug may be dispersed in different degree in the solid dispersion due to

different PVAc conformation. But additional analysis should be proposed to confirm this speculation.

Dissolution of the drug was prolonged as it was expected. The main reason for that is hydrophobic nature of polyvinyl acetate. Nevertheless that solid dispersion method was originally used to improve the dissolution rate and bioavailability of the drugs classified in the class II of the Biopharmaceustics Classification System in our study we wanted to reveal the possibility to develop controlled release solid dispersion to achieve the advantage for bypassing the risk of burst release of the drug. Thus it can be concluded from the given results that polyvinyl acetate could be easily used in those formulations. Additionally, an important effect on the release of the drug was the solvent used to prepare solid dispersion, as it has a great impact on the polymer conformation, thus influencing the properties of the spray drying outcome.

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