



# Solid dispersion systems for increase solubility: cases with hydrophilic polymers in poorly water soluble drugs

## Dispersões sólidas para incremento de solubilidade: casos com polímeros hidrofílicos em fármacos pouco solúveis em água

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### RESUMO

A utilização de novas técnicas para melhorar a solubilidade, taxa de dissolução e biodisponibilidade dos fármacos pouco solúveis em água é de grande importância no desenvolvimento de medicamentos, principalmente aqueles administrados por via oral. Entre estas, as dispersões sólidas (DS), sistemas estruturados de sólidos em que o fármaco está disperso em uma matriz biologicamente inócua, têm sido utilizados para aumentar a solubilidade de fármacos. Polímeros hidrofílicos também têm sido amplamente utilizados como carreadores por causa de seu baixo custo e alta solubilidade. No entanto, há poucos relatos de aplicação dessa técnica em um produto acabado, demonstrando a necessidade de conhecimento detalhado sobre as mais recentes técnicas de preparação mais utilizadas em laboratório e em escala industrial. O objetivo deste trabalho foi discutir os principais métodos utilizados na preparação e caracterização de DS, os fármacos que tiveram um aumento de solubilidade e as principais características físico-químicas dos polímeros hidrofílicos mais amplamente utilizados, listando suas vantagens e desvantagens.

**Palavras-chave:** Medicamentos, carreadores, dissolução, biodisponibilidade

### ABSTRACT

The use of new techniques to improve the solubility, dissolution rate and bioavailability of the poorly water soluble drugs is of great importance in the development of medicines, particularly those administered orally. Among these, the solid dispersions (SD), structured solid systems in which the drug is dispersed in a matrix biologically innocuous have been used to increase solubility of drugs. Hydrophilic polymers have also been widely used as carriers because of its low cost and high solubility. However, there are few reports of application of this technique into a finished product, demonstrating the need for detailed knowledge about the most recent major gathering techniques used in laboratory and industrial scale. The objective was to discuss of main methods used in the preparation and characterization of SD, the drugs had increased solubility and the main physicochemical characteristics of the most widely used hydrophilic polymers, listing their advantages and disadvantages.

**Keywords:** Medicines, Carriers, dissolution, bioavailability

### INTRODUCTION

Depending on its solubility in water, each drug has a different and only profile of release and action in the

target. The poorly soluble drugs require a technology for your release in specific target. Generally they present

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bioavailability problems, being the dissolution the limitant factor for the absorption of these drugs.

This property is so important that currently it is used as one of the criteria of biopharmaceutical classification (Figure 1). The factors that more influence in the drugs bioavailability, in formulations for oral administration, are solubility and permeability (Lipka & Amidon, 1999). The drugs solubility is controlled by superficial area that the particle presents for dissolution. The permeability in the biological membranes and the solubility/dissolution are essential factors to the effectiveness of drugs. This fact is considered a challenge for the pharmaceutical industry since more than 40% of active substances today investigated are presented insoluble or poorly soluble (Prentis *et al.*, 1998).

The absorption rate and the bioavailability of poorly soluble drugs are frequent controlled for the dissolution rate of drug in the gastrointestinal tract. So many times in the conventional treatment regimens is given a lot and a large fraction is excreted without any additional activity. Efficient alternatives that make drugs more available to a particular site of absorption rates with the most appropriate dissolution have been widely described in literature with the aim of increasing the solubility in aqueous systems, targeting drugs to specific sites of the body, releasing them in a way controlled and increase the therapeutic effect (Siler-Marinkovic *et al.*, 1997). The development of new techniques to improve the solubility, dissolution rate and bioavailability is of great importance in the development of pharmaceuticals, particularly those administered orally. Among these, the solid dispersions (SD), solid structured systems, in which the drug is dispersed in a matrix biologically innocuous in order to improve their oral bioavailability has been widely used to increase the solubility of hydrophobic drugs. They are obtained through a technological process that consists in dispersing a pharmacologically active component (drug) in a carrier or solid matrix in order to improve the solubility and stability, increasing the rate of dissolution, modulate therapeutic action, the properties sensory and permeability of drug through membranes absorptive (Habib, 2001). The choice of polymer or substance for the preparation of SD (besides the nature of the drug) will determine the dynamics of dissolution. Thus the association of the hydrophilic polymer with drugs poorly soluble in water determines the solubility and therefore increase dissolution. The objective was to evaluate the main drugs with limited solubility had their solubility characteristics through improved systems of SD, in addition to obtaining and characterization of the same and the use of hydrophilic polymers.

### SOLID DISPERSIONS

The term SD mentions a group of solid products composed for at least two components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be crystalline or amorphous. The drug can be molecularly disperse, in amorphous particles (clusters) or in crystalline particles (David, 2002).

In 1961, Sekiguchi e Obi had considered for the first time the formulation of a eutetic mixture to obtain to increase the dissolution speedy of a poorly soluble drug. In

this pioneering work, the authors prepare the mixture with sulfathiazole as poorly soluble drug model, and urea as hydrossoluble carrier. When being displayed to the water, the eutetic mixtures had been capable of release the drug more quickly, in the form of fine dispersion. Additionally, the gotten pharmaceutical forms, had presented greater bioavailability that the classic form (Santos, 2008).

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs (Dhirendra *et al.*, 2009). Currently if you prefer to use water soluble polymers as carriers, due to low solubility and general applicability to most drugs. A poorly soluble drug combined with a water soluble carrier system results in a quick release, while water-soluble drugs when combined with a slightly soluble carrier, resulting in delayed drug release (Chemtob, *et al.*, 1987).

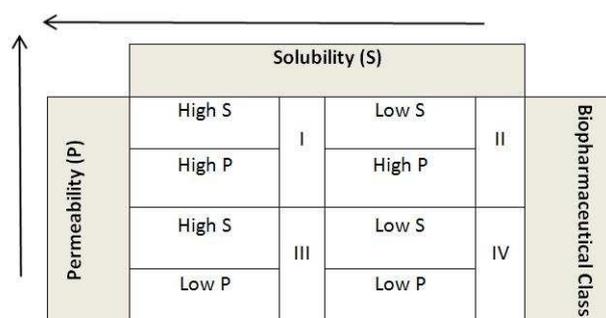


Figure 1. Biopharmaceutical classification system.

The development of SD as a practically viable method to improve the bioavailability of hydrophobic drugs overcame the limitations of previous approaches, such as salt formation, solubilization solvent and the reduction of particle size. Studies revealed that the drug in SD does not necessarily exist in the micronized state. A fraction of the drug could be molecularly dispersed in the matrix, thus forming a SD. When it is exposed to the aqueous environment, the carrier dissolves and the drug release occurring as fine colloidal particles. In addition, a portion of the drug dissolves immediately to saturate the fluid of the gastrointestinal tract and drugs to excess precipitate as fine colloidal particles (Van-Drooge *et al.*, 2006).

The mechanisms for the enhancement of the dissolution rate of SD have been proposed by several investigators. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers (Bobe *et al.*, 2011).

### MANUFACTURING PROCESS

SD prepared more often are amorphous and can be classified as solid suspensions, where the drug is dispersed in the matrix in the form of clusters, and solid solutions, where the drug is dispersed in a homogeneous manner at

molecular levels (Santos, 2008). Traditionally, SD are obtained by melting and by the method of solvent evaporation, but other technologies have also been used.

### Melting method

The fusion method was first proposed by Sekiguchi and Obi, and consists of blowing through a physical mixing the drug with the carrier followed by freezing and spray to get the product. The mixture is melted and rapidly cooled in order to obtain the supersaturation of the drug, whose molecules are trapped between the molecules of the carrier, due to rapid cooling does not allow the nucleation of the solute. Obtaining SD by the melt method can be limited by the thermal sensitivity of the constituents of the formulation (Santos, 2008) and can occur in this way the degradation of the drugs.

### Solvent evaporation Method

In the method of preparation by solvent evaporation, the carrier and the drug is usually dissolved in an organic solvent or gas in supercritical conditions, both stable, and the solvent is evaporated at a fixed temperature and reduced pressure. With the removal of the solvent is a supersaturation of the medium followed by simultaneous precipitation of the constituents. The solvent, adhered to the surface of the particle co-precipitate is removed by drying with the aid of vacuum. The method is illustrated in Figure 2, based on studies of Lima, 2008. This method is suitable for thermo labile drugs, which could degrade the melting temperature of the carrier. The difficulty of this method is finding a solvent that will dissolve both the drug and the carrier. Furthermore, the use of different solvents can induce the appearance of different polymorphs (Sethia & Squillant, 2003).



Figure 2. Attainment technique of solid dispersions by evaporation method in rotatory evaporator

### Atomization (Spray Drying)

The mixing part of the system and the rapid elimination of water provide a high efficiency of complexation. Moreover, this technique allows controlling the particle size obtained in very narrow ranges, fundamental, for

example, to obtain powder of pulmonary administration. The rapid cooling caused by low temperatures in liquid nitrogen and high degree of atomization results in amorphous nanoparticles. Helium, propane, other cryogenic liquids such as argon and diidrofluorethers or silicon dioxide can be employed to spray. The low yield and thermal stress are some limitations of this technique (Fernandes & Veiga, 2002). Figure 3 illustrates the method of obtaining SD by spray drying, where the dispersed particles are already formed with small size and homogeneous.

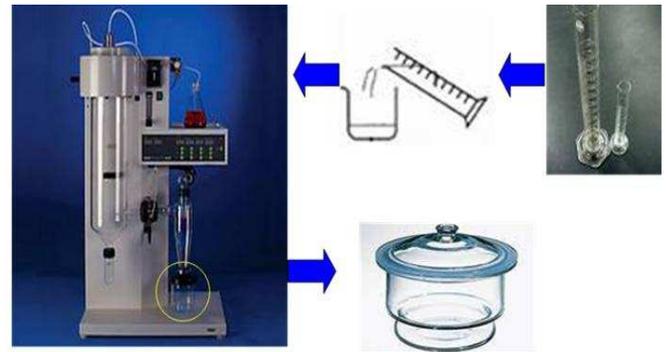


Figure 3. Attainment technique of solid dispersions by atomization method by spray drying.

### Liophilization

This technique was proposal as one alternative technique to the evaporation of the solvent. The freeze was intended as a molecular technique, which consists in removing solvent systems in solution, through a prior freezing and subsequent drying at reduced pressure to obtain a lyophilized molecular dispersion. It has certain disadvantages, the long processing time and poor flow characteristics of the material obtained (Rodriguez-Perez *et al.*, 2006).

### Co-precipitation method

This technique is part of a solution of the drug in conditions of near saturation and by changes in temperature or addition of organic solvents, one obtains the precipitation of material in the form of inclusion complex. The crystals obtained were collected by centrifugation or filtration (Miro *et al.*, 2000). This method is widely used in laboratory scale. However, the low yield achieved at larger scales, the risk of formation of inclusion complexes with organic solvents and the long processing time (one to three days) makes it unattractive industrial scale.

### Emulsification method

In this method, the drug - dispersed in an organic solvent - is dispersed in an aqueous phase containing surfactant. This step is followed by evaporation of organic solvent on reduced pressure (rotaevaporation), which results in precipitation of the drug particles to form a suspension of nanoparticles, which is stabilized by the addition of surfactant. The emulsification should not be used for drugs that have low solubility in both media employees (aqueous or organic). Besides being restricted to drugs that not tolerate changes in temperature, even if those changes are

small.

### Supercritical fluidization

Is one of the most innovative methods of obtaining complexes in the solid state. The design of particles using supercritical carbon dioxide (CO<sub>2</sub>) gives the materials obtained by this technique, unique features about the interaction. In the process, the supercritical CO<sub>2</sub> is blended with organic solvent containing the drug. The solvent expands in supercritical CO<sub>2</sub>, thus increasing the concentration of solute in solution, resulting in a supersaturated solution, causing precipitation of the solute. Microparticles and nanoparticles are formed after the precipitation of the drug by the mass transfer due to the extraction of organic solvent with the CO<sub>2</sub>. The high mass transfer is important to minimize the agglomeration of particles and reduce the drying time. Despite being a nontoxic method (do not use organic solvents), fast, chemically stable (using moderate temperatures), low maintenance cost and with promising results described in the literature, it is still an experimental technique and presents an initial high (AL-Marzouq *et al.*, 2007).

### Kneading method

It consists of a paste from the addition of minimum amount of liquid (water or aqueous-ethane mixtures) enough to moisten the powder mixture of drug and polymers. In laboratory scale, is performed in a mortar with the aid of a pistil (Lima *et al.*, 2008), as illustrated in Figure 4. Industrially, the mixture of components is performed in a kneading shaft mounted off. The drying of the material can be made into glass or directly into the kneading shaft mounted off followed by spraying for a uniform particle size. Variations of this technique using heat or extruders granulators fluidized bed are reported (Choudhary *et al.*, 2009).

Due to its simplicity, high efficiency and ease of implementation of scale, this method is one of the most used in the pharmaceutical industry.

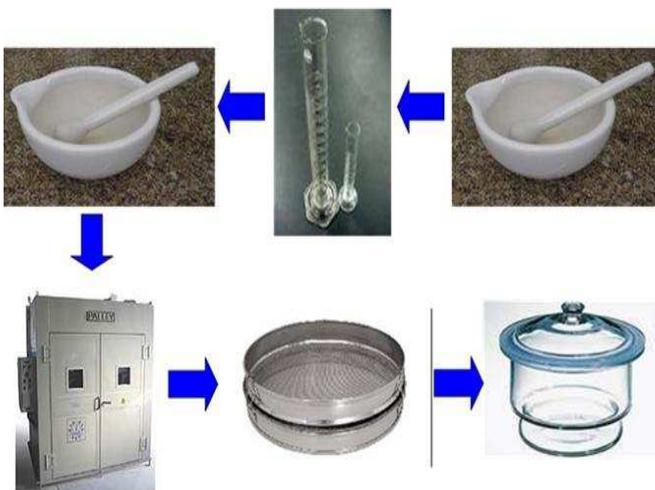


Figure 4. Attainment technique of solid dispersions by kneading method

## CHARACTERIZATION OF SOLID DISPERSIONS

The methods used to characterize the substances in solid form, and its behavior in aqueous media can be performed *in vitro* or *in vivo*. Usually employ spectral techniques that are based on the interaction of condensed matter with radiant energy or using techniques for observing the behavior of the substance when subjected to heat or solvent action (Santos, 2008). The most important methods to characterize the SD are: Infrared spectroscopy (IR), x-ray diffraction, thermoanalytical methods, dissolution studies on drugs and scanning electron microscopy (SEM).

### Infrared spectroscopy (IR)

Infrared spectroscopy has been used to identify the nature and extent of chemical interactions that occur in SD (Van den Mooter *et al.*, 2001). Using this method assumes that the mixing of two components at the molecular level should lead to changes in the oscillations of the dipole molecules. These changes are manifested in the spectrum in the form of changes in the frequency and width of the bands of interacting groups. Thus, if the functional groups of drug and polymer interact, then the infrared spectrum of the groups will present the bands shifted and flattened when compared with the spectra of individual components of the mixture.

### X-Ray Diffraction

Among the crystallographic techniques, the x-ray diffraction is the most used due to its simplicity and speed. Each profile provides a crystalline compound diffraction characteristic, consisting of peaks, ridges being equivalent to the radiation incident. From the standard diffractogram and the total area under the diffraction peaks, it becomes possible to identify the crystalline form and degree of crystallinity of a sample. Moreover, amorphous solids exhibit a diffractogram peaks without defined (Santos, 2008). Therefore, it is possible with X-ray diffraction to differentiate between SD in which the drug is amorphous, and solid dispersions, which is at least partly present in crystalline form, regardless of whether the carrier is amorphous or crystalline (Verheyen *et al.*, 2002). With this technique it has become an indispensable tool for characterizing the degree of crystallinity of solids, and has been used in virtually all work involving the characterization of SD (Van den Mooter *et al.*, 2001).

### Thermoanalytical methods

Thermal methods of analysis are made by techniques that measure changes in physical and chemical properties of substances as a function of temperature. Despite some limitations and the need to use other complementary techniques for more precise information, this test can, in many cases, provide quantitative information about the degree of complexation, as well as valuable information on the stability of the system and their crystallinity. The most widely used techniques in the characterization of SD are thermogravimetry, differential thermal analysis and differential scanning calorimetry. Among these, differential scanning calorimetry (DSC) is the most used method because it allows quantitative detection of all cases in which energy is required or produced. The usual method

of measurement is the heating of the test and reference samples so that the temperature of the two is maintained. The lack of a peak in the DSC melting a SD indicates that the drug is present in more amorphous state than in crystalline form. Since the method is quantitative, the degree of crystallinity can also be calculated for systems where the drug is partly amorphous and partly crystalline (Kreuter, 1999). The methods of thermal analysis have been widely employed in the characterization of mixing of polymers with drugs, usually to determine the temperature and enthalpy of melting and recrystallization, which are parameters that help to elucidate the interactions that occur in the formulation and to assess the crystallinity material (Van-Drooge *et al.*, 2006).

#### Dissolution studies

The dissolution tests *in vitro* can compare lots of different formulations or different compositions and are fundamental step in the development and quality control of pharmaceutical preparations. Usually the dissolution tests *in vitro* are influenced by the solubility of the drug in the solvent, particle size distribution, shape and pharmaceutical excipients used (Santos, 2008). A well-developed dissolution experiment show that the solubility and dissolution rate of drugs was improved, and whether the supersaturated solution is stable or tends precipitate rapidly. Comparison of results from the dust of the pure drug and physical mixtures of drug with the carrier can help indicate whether the carrier has improved the dissolution by the formation of SD (Verheien *et al.*, 2002).

#### Scanning Electron Microscopy (SEM)

The scanning electron microscopy is used in various fields of knowledge, being widely used to study the structural aspects of materials. Use of this technique is becoming more frequent for detailed information, with increases of up to 300,000 times, the state of crystallization of products obtained by different techniques of complexation and SD (Duarte *et al.*, 2003).

Detailed knowledge of the microstructure of materials allows the understanding and in many cases, even the prediction of the properties and behavior of the same. From the SEM, we evaluate the contribution in terms of decreasing the crystallinity of the particles obtained through the various methods for forming SD, as it allows the visualization and differentiation of particles of polymers and crystals of drugs (Pralhad & Rajendrakuma, 2004).

In general, the polymer particles are globular and amorphous, while the drugs are presented in the form of crystals smaller, irregularly shaped, but with a distribution of particle size more homogeneous. In physical mixtures is usually possible to distinguish the particles of drug particles of polymers, according to studies of Lima, in 2008, displayed in Figure 5. A photomicrograph through a physical mixture of drug benzimidazole (BNZ) with the polymer polyethylene glycol (PEG) where there is clearly elongated crystals, large and well-defined BNZ mixed crystals smaller and irregularly shaped PEG. In the case of SD, the resulting crystalline state is different from that obtained by simple mixing of the drug and the polymer

molecule. This is shown in Figure 5B, where it has a photomicrograph of a SD between BNZ and PEG, where the drug loses its crystalline structure is well defined and confused BNZ and PEG crystals with irregular shapes.

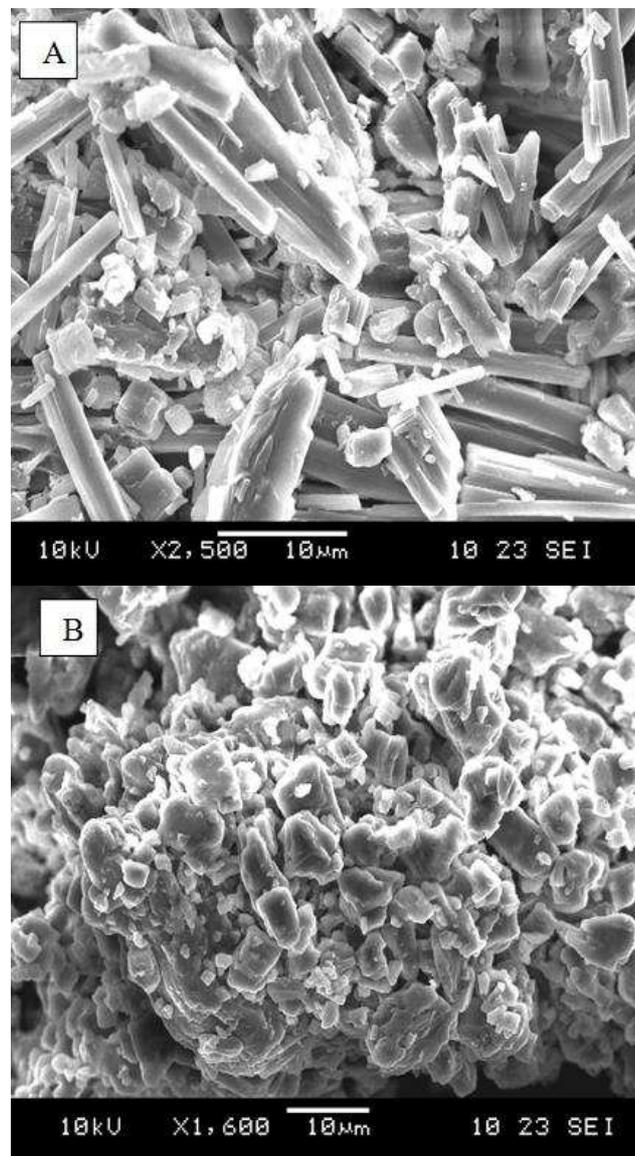


Figure 5. SEM photomicrographs of physical mixture BNZ-PEG (A) and solid dispersion BNZ-PEG (B)

#### HYDROPHILIC POLYMERS

The improvement in the development of modified release systems depends on the selection of an appropriate agent capable of controlling the drug release, maintaining therapeutic action over time and / or releasing the drug at a particular tissue or organ. Within the various options, the polymers are versatile and promising agents to perform such a function (Lordi, 2001).

Thus, the use of matrix systems consisting of various types of polymers is an interesting option, one of the best strategies used to develop a modified release oral formulation due to the advantages inherent in such systems: versatility, efficiency, and low cost production uses equipment and techniques. Furthermore, the use of

matrix systems allow the incorporation of relatively large quantities of drugs.

Among the more hydrophilic polymers reported in literature for preparation of SD have the polivinylpirrolidone (PVP), polyethylene glycol (PEG) and hidroxipropilmethylcelulose (HPMC).

#### Polivinylpirrolidone (PVP)

Polivinylpirrolidone commonly known as PVP (Figure 6) is a highly hydrophilic polymer found in the market with specifications of average molecular weight varying from 2.5 to 3000 kDa, expressed as a function of the value K.

This polymer is widely used as a pharmaceutical excipient in combination with a wide variety of drugs being used in various pharmaceutical forms for different purposes. This versatility combined with low toxicity justifies the use of PVP to obtain SD. PVP has glass transition temperature relatively high, above 110°C, which limits their use in obtaining SD by fusion method. However, due to its solubility in a wide variety of solvents, this polymer is widely used and studied to obtain solid dispersions by solvent evaporation method. Some studies have shown that PVP inhibits the crystallization in SD hydrogen bonding, hence inhibits the nucleation and crystallization.

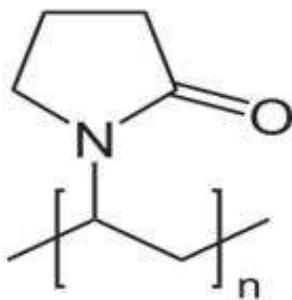


Figure 6. Chemical structure of PVP monomer

#### Polyethylene glycol (PEG)

PEG (Figure 7) presents various molecular weights and different melting temperatures, and this is one reason for being widely used in many industrial applications involving heating. Its molecular weight ranges from 200 to 300.000 (PATEL *et al.*, 2008). Ordinarily, the preparation of SD and solutions are used PEGs with molecular weights between 1.500 and 20.000. With increasing molecular weight of PEG, there is the elevation of its viscosity and its melting point. In the structures of molecular weight of 600, the PEGs are fluid, in the range between 800-1500 has a higher consistency, between 2000-6000 have aspects waxy and those with molecular weights above 20.000 are in the form of fragile crystals at room temperature.

#### Hidroxipropilmethylcelulose (HPMC)

HPMC (Figure 8) is a linear hydrophilic polymer and the works conducted show that its effects are manifested mainly by their ability, after hydration, swell and form a gelatinous layer on the surface of the tablet. This functions

the barrier to the fast release of drug, controlling the penetration of water and the speedy release of active substance (Colombo *et al.*, 1999).

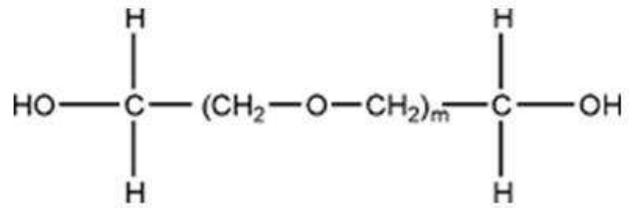


Figure 7. Chemical structure of PEG monomer.

The ample use of HPMC matrices it must the existence of great variety of this polymer, that it's classified accordance with your viscosity and the proportion between substituent groups (methoxyle and hidroxypopile groups). The hydration degree of this hydrosoluble polymer depends of physical-chemistry characteristics, as molecular mass, the substitution degree and the viscosity. One of the characteristics most important of this hydrophilic polymer with regard to its application in controlled delivery systems is the ability of swelling / relaxation, which exerts pronounced effect on the release kinetics of the drug incorporated. Its popularity is due also to other characteristics such as non-toxic and non-ionic polymer (showing no compatibility problems), the ability to incorporate large amounts of active ingredients, the simplicity, speed and economy technology associated with its preparation and the possibility of fabrication of matrix tablets by direct compression with good compression characteristics without prior granulation step (Rodriguez *et al.*, 2000).

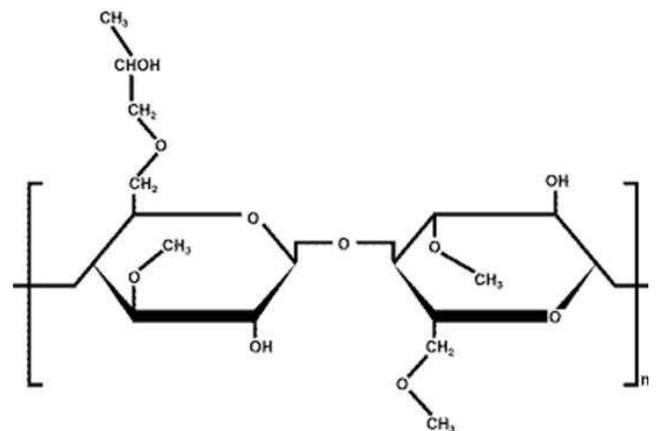


Figure 8. Chemical structure of HPMC monomer.

### CASES OF APPLICATION OF SOLID DISPERSIONS IN PHARMACEUTICAL AREA

The search for systems that perform complex tasks in restricted regions of the human body and can be controlled and manipulated has stimulated research in various fields of pharmaceuticals. The alternative found to improve the rate of solubility and dissolution rate of poorly soluble drugs has been the association of these drugs in appropria-

te delivery systems.

According to Souto *et al.* (2008), Fluconazole (FLC), a synthetic drug derived from triazole, used to treat cutaneous and systemic fungal infections, and also used in prevention and treatment of fungal infections is considered a drug of low solubility and high permeability. The technique used to improve the solubility of SD was obtained by dispersion of the drug in the presence of PVP. Comparing the dissolution profile of pure FLC and of the solid dispersion, it is clear the increased rate of dissolution of the drug in SD (about 38% over the final 90 min). So it is possible to attribute this improvement in dissolution properties of the FLC to the use of pharmaceutical technology employed.

According to Verheyen *et al.* (2002) the use of formulations of hydrochlorothiazide SD in PVP, the method of solvent evaporation, contributed to increased drug solubility in water, justified by the formation of amorphous solid structure, which keeps the system stable through hydrogen bonds and a plasticizing effect, similar to the effect exerted by PEG 6000 on benzodiazepines (Santos, 2008).

Studies with Efavirenz had significant results when combined with PVP K-30 made possible the preparation of ternary systems of SD in a solid form, which would make possible the preparation of dispersions of consistency best suited for the production of solid dosage forms, as well as the use of simpler methods and higher yield for the preparation of the DS, as the method of mixing, which could be more easily transferred to an industrial scale (Alves, 2009). Solid dispersions of Praziquantel (PZQ) were obtained by precipitation in the presence of PVP. There was an increase in solubility and dissolution profile of the drug, showing that the presence of the carrier significantly increases the amount of PZQ dissolved and the SD exhibit a dissolution profile rather than the physical mixtures. The highest rate of dissolution of SD in PZQ is probably due to increased interaction of the drug with the carrier resulting in the change of amorphous to crystalline state (Lima, 2008).

Using technology to obtain SD to provide increased solubility of  $\beta$ -lapachone is an unprecedented fact in the scientific field. The results indicate that the use of PVP K-30 and PEG 4000, hydrophilic polymers, such as carriers, through the technique of SD, improves the water solubility of  $\beta$ -lapachone and dissolved content, and may improve their bioavailability by reducing the size the particles increase the surface area of contact, improve wettability and lead to an amorphous compound (Alves, 2008).

Surface SD technique has been extensively used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs such as ibuprofen, piroxicam, meloxicam, itraconazole and ursodeoxycholic acid (Kiran, *et al* (2009)).

Sinha *et al* (2010) indicated that the SD prepared by solvent evaporation method is a promising approach for the bioavailability enhancement of ritonavir and can be used for the solid dosage form development for oral use in order to commercialize.

Rao *et al* (2010), used SD with two different carriers in

three different drug-carrier ratios were prepared by a coevaporation method, evaluated for different parameters, and further evaluated for in vivo performance in albino rats using pharmacodynamic markers such as total cholesterol (CH), triglycerides (TG), low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL). In vivo studies in rats showed a higher percentage inhibition of cholesterol and triglyceride levels in rats than those achieved with plain drug. This is attributed to improved bioavailability due to enhancement in rate and extent of drug release when drug was administered as an SD using croscarmellose sodium as a carrier.

According to Bley *et al* (2010), SD were prepared by a melting method from the water-insoluble model drugs carbamazepine and nifedipine and polyethylene glycol 1500 (PEG 1500) or 1:1 mixtures of PEG 1500 and the polymers polyvinylpyrrolidone (PVP 30, PVP 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA) and Eudragit EPO (Eudragit) in order to combine advantages of the different carrier polymers (recrystallization inhibition, processability and stability). The most stable solid dispersion concerning dissolution rate and stable amorphous drug was the drug/PEG 1500/PVPVA solid dispersion for both drugs followed by the PEG 1500/PVP 30, PEG 1500/PVP 12 and PEG 1500/Eudragit solid dispersions.

According to Lima (2008) and Lima *et al* (2011), increased solubility and dissolution rate of BNZ could be achieved by the formation of SD with PVP K30 and PEG 6000 obtained by the method of kneading. Based on the results could be seen that the solid dispersions were very effective in improving these characteristics, which are limiting points of this drug and impair its bioavailability. In this work were conducted molecular modeling studies between these polymers PVP and PEG and BNZ, where they were designed tri-dimensional chemical structures of polymers and drug for further theoretical study of interaction drug-polymer SD in PVP-PEG-BNZ and BNZ, according to Lima (2011), in figure 9. The objective was to determine which of the two systems would be greater interaction and interaction between the polymer BNZ, reporting through a theoretical study, a result which eventually will be confirmed with other characterizations of SD.

Ghosh *et al* (2011) developed a physically and chemically stable amorphous SD of a poorly water-soluble compound, NVS981, which is highly thermal sensitive and degrades upon melting at 165 °C. Hydroxypropyl Methyl Cellulose (HPMC) based polymers; HPMC 3cps, HPMC phthalate (HPMCP) and HPMC acetyl succinate (HPMCAS) were selected as carriers to prepare solid dispersions using hot melt extrusion because of their relatively low glass transition temperatures. The SD were compared for their ease of manufacturing, physical stability such as recrystallization potential, phase separation, molecular mobility and enhancement of drug dissolution. In conclusion, of the 3 polymers studied for preparing solid dispersions of thermally sensitive compound using hot melt extrusion, HPMCAS was found to be the most promising as it was easily processible and

provided stable solid dispersions with enhanced dissolution

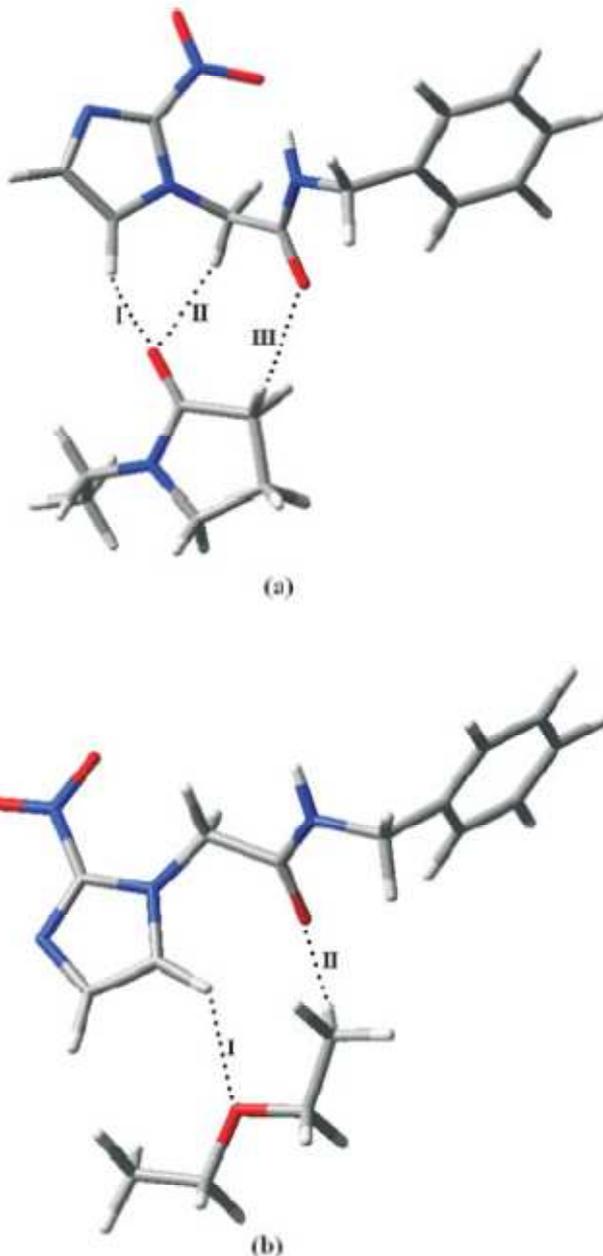


Figure 9. Optimized geometris obtained for the PVP-BNZ (a) and PEG-BNZ (b) complexes after calculations

## CONCLUSION

The low solubility of drugs continues being the great difficulty of the medicines development with molecules of vast therapeutical potential. The most of the new chemical entities are poorly soluble drugs, that can present reduced therapeutical effect due to its low bioavailability. SD are one of the most attractive processes to improve the solubility of poorly soluble drugs, the stability and performance by increase of solubility through drug-polymer interaction, loss of crystalline structure, increase

of wettability e particle porosity. In this work had been show, beyond a detailed boarding of attainment methods and characterization, some cases of application of SD with hydrophilic polymers and its importance to the increase of solubility/dissolution of drugs. Through this work, it was possible to confirm the great relevance of these systems for the pharmaceutical technology, also on improve of physical chemical characteristics of drugs or new chemical entities for the medicines development.

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