Physico-Chemical Characterization of Drugs: Acidity and Solubility

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CHAPTER 4

Solubility and enhancement of dissolution rate of a poorly water soluble drug, the Amphotericine B

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4.1 INTRODUCTION

Many new drug substances have low aqueous solubility which can cause poor bioavailability after oral administration. Bioavailability refers to the extent and rate at which a drug reaches the systemic circulation after administration. When the drug is administered via the intravenous route, the bioavailability is considered to be 100%. However, most of the drugs are administered via other routes, such as the oral route. The bioavailability of these drugs is often incomplete due to poor dissolution which causes the incapability to permeate the absorbing membrane or metabolic transformation during the absorption process. It should be noticed that several drugs yield erratic absorption after oral administration caused by incomplete dissolution in the gastrointestinal lumen when administered in a solid dosage form [1].

Most of new drugs can be classified according to the Biopharmaceutical Classification System (BCS) as class II drugs (see general introduction). These drugs show a poor aqueous solubility but once dissolved they are highly absorbed over the gastro-intestinal membrane [2]. Therefore, the dissolution rate of the drug determines its bioavailability after oral administration [3]. There are many strategies to increase the dissolution rate of poorly soluble drugs. Classical approaches include, amongst others, particle size reduction, *pH* adjustment, salt formation, the use of co-solvents, complexation, addition of surfactants, formulation as emulsion or other lipid based systems or entrapment in liposomes [4]. However, many of these techniques are limited to specific drugs or formulations. For instance, *pH* adjustment is only effective for drugs with acid-base properties and salt formation can only be applied to ionizable drugs. Co-solvents are often needed in too large amounts. The use of complexing agents such as cyclodextrins is limited to molecules that fit in the cyclodextrin conus. Large amounts of surfactants are not well tolerated and the entrapment capacity of liposomes is limited. Another frequently described approach to enhance the dissolution rate is the application of solid dispersions that is a drug present in the amorphous state and/or as small crystals, incorporated in a carrier or matrix. BCS class IV drugs may also benefit from the use of solid dispersions. However, the bioavailability of these drugs is limited because of both a poor solubility as well as a poor permeability.

Although in general the improved dissolution rate will not improve the poor permeability, the overall bioavailability of these drugs may increase due to the improved dissolution behavior provided by the solid dispersions [5].

The aim of this study is to investigate the dissolution behaviour of pharmaceutical formulations containing a potent antifungal, Amphotericine B, prepared from physical mixtures or from solid dispersions. Both physical mixtures and solid dispersions should contain, at least, a carrier and in some cases a surfactant. In some instances, the presence of a desintegrant is also tested in order to look for the best composition for tablets of Amphotericine B. Here, the best composition means the one that allows the maximum drug release in a reasonable period of time and, then, its best bioavailability. Thus, compounds used have been:

Amphotericine B is a very potent antifungal antibiotic, usefull in the treatment of many mycotic infections. Despite its toxicity, it is the most relaible drug in the treatment of most life-threating fungal infeccions. It has got very poor bioavailability. Its solubility in water is rather poor and it causes problems in a suitable oral liquid formulation. Amphotericine B can be well-dissolved in liposomes, due to its amphipathic (having hydrophobic and hydrophilic regions) characteristics. The infusion formulations of Amphotericine B are the most popular in clinical practice, but no oral formulation for treating the systemic infections has been recommended till now. The severe acute side toxicity of Amphotericine B deoxycholate includes nausea, vomiting, rigors, fever, fatigue, chills, swelling, liver disease, kidney problems, hypertension or hypotension, electrolyte abnormalities and hypoxia. Lungs or heart problems are less common but more severe. The most severe chronic adverse effect of Amphotericine B is nephrotoxicity. These adverse effects limited clinical applications of Amphotericine B. Fungizone® (Bristol-Myers Squibb, NY, USA) is a traditional formulation of Amphotericine B for intravenous infusion and has populated since 1970s. It is a colloidal dispersion with sodium deoxycholate, which involves intravenous administration over 6 weeks. Several months of therapy are sometimes necessary. In the stability study, vials of amphotericin B powder for injection should be stored in the refrigerator (2-8)°C, protected from light and moisture.

Inulin and **mannitol** have been selected as carriers since they have great use and are very economic. Inulin is used such as a vehicle in drug delivery, as a diagnostic/analytical tool or as a dietary fibre with additional health benefits. In the main, much research has focussed on inulin as a drug delivery carrier for colon-targeted drug delivery. The justification for this is its potential to survive the stomach's acidic environment. This unique stability and strength is utilized in many ways to deliver drugs safely to colon, where they can be easily absorbed through the gut epithelium into the blood. Mannitol is industrially derived from the sugar fructose, and is roughly half as sweet as sucrose. Mannitol has a cooling effect often used to mask bitter tastes, and may be used in gums and candies. Mannitol is also found naturally in many species, including plants, bacteria, and fungi. Excessive consumption of mannitol may lead to a laxative effect, but the small amount used in pharmaceutical manufacturing processes would not normally pose this risk. Mannitol is deemed a safe food ingredient and it has various applications. Thus, it is widely used in the management of raised intracranial pressure (ICP), for renal protection in cardiac, vascular, and renal transplantation surgery, and in the management of rhabdomyolysis. Also it is often used in tablet filler. In this study mannitol was used as tablet fillers (10% to 90%), due to its non-hygroscopic character, so for the water-sensitive tablet drugs particularly valuable [6].

Sodium deoxycholate (SDC) and Sodium lauryl sulfate (SLS) surfactants were used: Sodium Deoxycholate is an ionic detergent that is especially useful for disrupting and dissociating protein interactions. In this study, sodium deoxycholate (deoxycholic acid) is a water-soluble, bile-acid and ionic detergent commonly used in protein methods. It is most frequently used as a component of cell lysis buffers (e.g., RIPA buffer), but also has been used for liposome preparation, isolation of membrane proteins and lipids, preventing nonspecific binding in affinity chromatography and a cell culture media supplement. Sodium lauryl sulfate (SLS) is an anionic surfactant used in many cleaning and hygiene products. It is derived from inexpensive coconut and palm oils and it is a common component of many domestic cleaning products.

Primojel was tested as disintegrant. Disintegrants are substances or mixture of substances added to the drug formulation that facilitate the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of

disintegrants. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. The disintegrants have the major function to appose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared [7].

4.1.1 Dissolution of a pure solid

A description commonly used to explain the dissolution of a solid, was originally developed by Noyes and Whitney [8]. They claimed that the dissolution rate was proportional to the difference between bulk concentration and concentration at the dissolving interface. Nernst and Brunner [9] were the first to propose the diffusion layer model. They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk is completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface. These assumptions are depicted in Fig. 4.1.1.

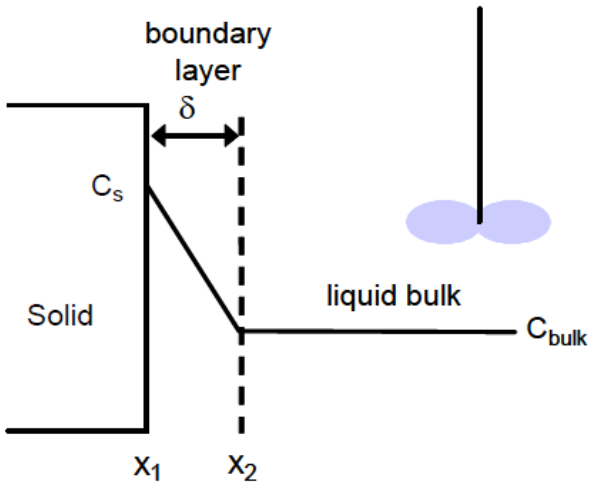


Figure 4.1.1: Schematic representation of dissolution of a solid

The dissolution rate of a solid is given by Noyes and Whitney Equation (Eq. 4.1.1):

$$\frac{dm}{dt} = A\frac{D}{\delta}\left(C_s - C_{bulk}\right) \qquad [4.1.1]$$

In which dm/dt is the dissolution rate ($kg \cdot s^{-1}$). In fact, all five parameters at the right-hand side of the equation can be affected in order to accelerate the dissolution rate.

A represents the surface area available for dissolution. Micronization of drug particles increases the surface area and has been shown to accelerate dissolution [10].

D is the diffusivity of the dissolving compound. A high diffusivity establishes fast transport through the stagnant layer. The diffusivity in solutions can be calculated by the Einstein-Stokes relation (Eq. 4.1.2):

$$D = \frac{KT}{3\pi\eta d} \qquad [4.1.2]$$

in which η is the dynamic viscosity of the medium, i.e. the viscosity of the solvent in the boundary layer, and d is the diameter of the diffusing molecule, k is the Bolzmann constant and T is the temperature. Therefore, for a certain drug and temperature, only the viscosity of the medium can be used to change the diffusivity. Preferably, matrices that give only a minor or no increase in the viscosity in the boundary layer should be used.

δ is the thickness of the stagnant layer. To achieve an efficient diffusion, δ should be minimized. This layer becomes thinner as the bulk surrounding the solid is stirred more vigorously, e.g. *in-vitro* when the rotation speed of the impeller (ω in eq. 3 in s^{-1}) is increased or in-vivo when the intestinal mobility is higher. However, according to Nelson [11] also a low dynamic viscosity (η), and a high density (ρ) of the dissolution medium minimizes the diffusion-layer thickness (Eq. 4.1.3):

$$\delta = \sqrt{\frac{\eta}{\rho\omega}} \qquad [4.1.3]$$

C_s stands for the drug solubility in surface (C_s). An increase in C_s accelerates the dissolution.

C_{bulk} is the concentration of drug in the bulk.

4.1.2 Dissolution of a binary solid

The Noyes and Whitney equation (Eq 4.1.1) is applicable for pure solids but the dissolution of a binary solid is more complex. The dissolution rate of two components, intimately mixed in solid dispersions, mutually affect each other. Higuchi [12] investigated a uniform, intimate, non-disintegrating mixture of two dissolving compounds both in crystalline state. One of the compounds (e.g. the matrix (carrier)) dissolves faster, resulting in a porous layer containing of the other compound (e.g. the lipophilic drug) (see Figure 4.1.2).

However, the developed model shows several weaknesness and then, it results at a limited usefulness [12-17].

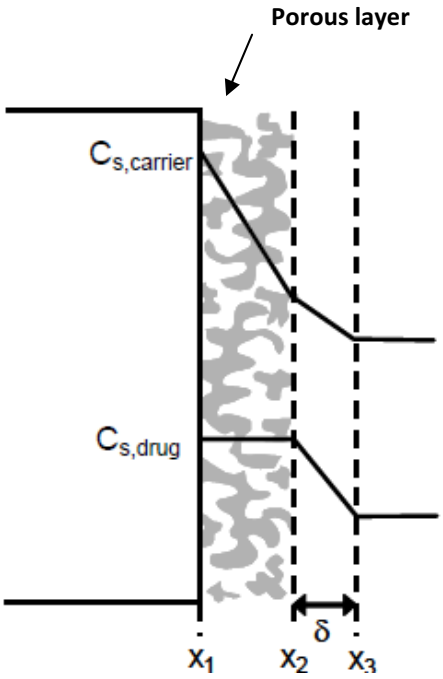


Figure 4.1.2: Schematic representation of dissolution of a binary mixture

4.1.3 Physical mixtures and solid dispersions

The term physical mixture refers to a mixture prepared from at least two different components, generally a hydrophilic matrix and a hydrophobic drug, by mixing them manually by means of spatula.

The term solid dispersion refers to solid products of the same composition of physical mixtures but prepared in a particular way described later. In this instance, the matrix can be either crystalline or amorphous, and the drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles (Fig. 4.1.3). Based on their molecular arrangement, different types of solid dispersions can be distinguished and, also, certain combinations can be encountered, i.e in the same sample, some molecules present in clusters while some are molecularly dispersed. Knowledge about the molecular arrangement will facilitate optimization of the properties required for a specific application.

To investigate the molecular arrangement in solid dispersions, many techniques are available which are able to detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample.

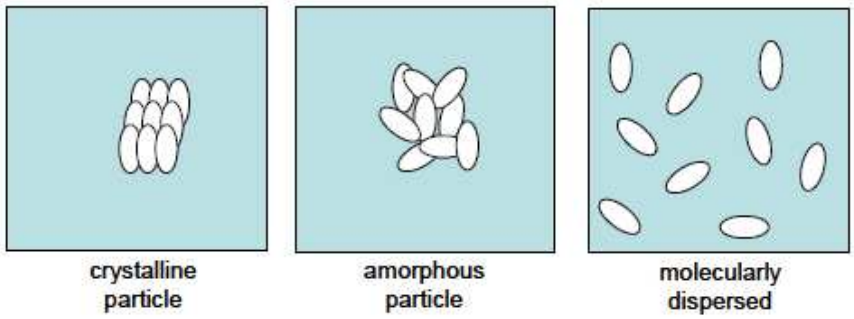


Figure 4.1.3: Schematic representation of three modes of incorporation of the drug in a solid dispersion

The technique used in this work to detect crystallinity in solid dispersion was Powder X-ray diffraction that can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate the presence of crystalline material.

The mechanism of dissolution rate enhancement of a lipophilic drug incorporated in a solid dispersion is still to a large extent unclear. Publications on the fast release of drugs from solid dispersions are ubiquitous, but Craig [18] stated that only few of them focus on the mechanism of release and the parameters that dominate the dissolution process. However, it should be pointed out that in solid dispersions, the drug should be dispersed in particles as small as possible, preferably mono-molecularly. Moreover, the large surface area of the drug during dissolution of a solid dispersion can be maintained by matrices since they prevent agglomeration of small drug particles [19].

4.1.4 Preparation of solid dispersions by freeze drying method

The freeze drying method is very useful to prepare solid dispersions. Freeze drying, also known as lyophilization, is widely used for pharmaceuticals to improve the stability and longterm storage stability of labile drugs, especially protein drugs. Freeze-dried formulations not only have the advantage of better stability, but also provide easy handling (shipping and storage). An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most significant advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. A typical freeze-drying process consists of three stages; that is, freezing, primary drying, and secondary drying. Freezing is an efficient dessication step where most of the solvent, typically water, is separated from the solutes to form ice. As freezing progresses, the solute phase becomes highly concentrated and is termed the “freeze concentrate.” By the end of freezing, the freeze concentrate usually contains only about 20% of water (w/w), or less than 1% of total water in the solution before ice formation. The freezing stage typically takes several hours to finish. Primary drying, or ice sublimation, begins whenever the chamber pressure is reduced and the shelf temperature is raised to supply the heat removed by ice sublimation. During primary drying, the chamber pressure is well below the vapor pressure of ice, and ice is transferred from the product to the condenser by sublimation and crystallization onto the cold coils/plates (<−50°C) in the condenser. Typically, the primary drying stage is the longest stage of freeze drying and optimization of this stage has a large impact on process economics. Secondary drying is the stage where

water is desorbed from the freeze concentrate, usually at elevated temperature and low pressure. Some secondary drying occurs even at the very beginning of primary drying as ice is removed from a region, but the bulk of secondary drying occurs after primary drying is over and the product temperature has increased. Secondary drying normally takes only some hours, and the opportunity for time reduction by process optimization is limited. With an optimum freeze-drying process, the freeze-drying process is optimized for all the three stages[20].

4.1.5 Physical stability of amorphous solid dispersions

The dissolution behaviour of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure and, in addition, the molecular mobility should be as low as possible. However, solid dispersions, partially or fully amorphous, are themodynamically unstable [21]. Thus, in solid dispersions containing amorphous drug particles, the drug can crystallize, but a nucleation step is required prior to that and it involves the migration of the drug molecules through the matrix. Therefore, physical degradation is determined by both diffusion and crystallisation of drug molecules in the matrix. It should be noted that in this respect it is better to have a crystalline matrix, because diffusion in such a matrix is much slower. Physical changes are depicted in Fig. 4.1.4

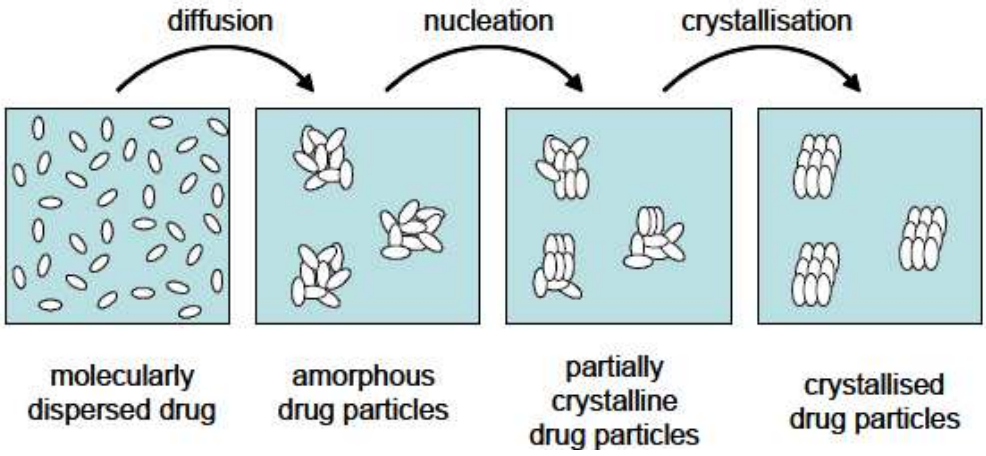


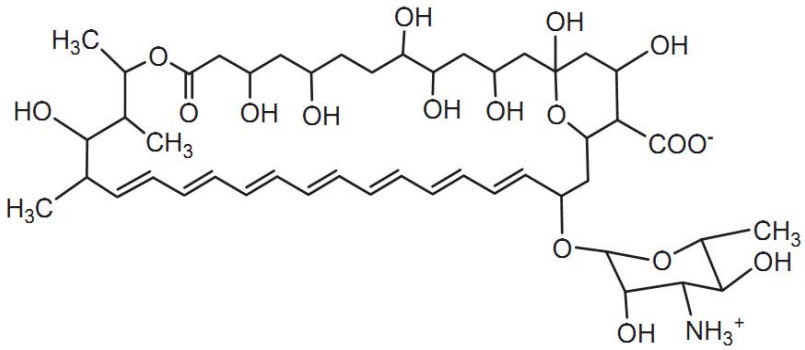
Figure 4.1.4: Physical changes in solid dispersions resulting in crystallization

4.2 EXPERIMENTAL

4.2.1 Chemicals

Drug

Amphotericine B structure has a rigid nonpolar heptane unit in one side, and a flexible polar polyol region. A mycosamine group which includes an amino group and one carboxyl group locate at one end of the molecule. These two groups are both charged in neutral *pH*. It was provided from (BUFA B.V. Uitgeest, The Netherlands).

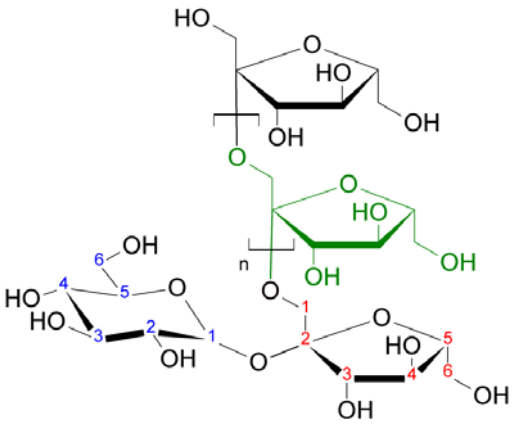


Some physical properties of Amphotericine B given in literature are:

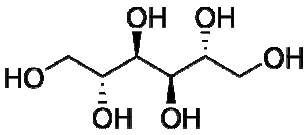
Melting point: 170°C [23], Apparent oil/water partition coefficient: 56.95 [24], Aqueous solubility at 37°C: 33.97mg/L [24], $\log P_{o/w\ calculated}$: -3.65 [25], pK_a: 5.7 (COOH), 10.0 (NH_2) [26].

Carriers

Inulin is a group of naturally occurring polysaccharides produced by many types of plants which belong to a class of fibers known as fructans. Inulin is used by some plants as a means of storing energy and is typically found in roots or rhizomes. Most plants that synthesize and store inulin do not store other materials such as starch. It was inulin kDa provided from (Sensus, Roosendaal, The Netherlands).



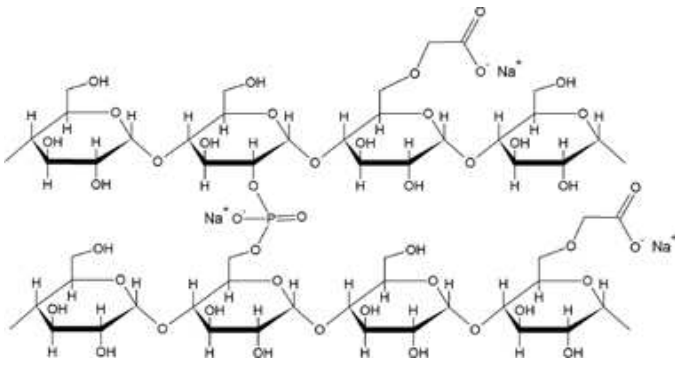
Mannitol: Mannitol is a polyol (sugar alcohol) and an isomer of sorbitol. Mannitol ($C_6H_8(OH)_6$) is used in pharmaceutical products as a sweeting agent, tablet and capsule diluent, excipient for chewable tablets, a tonicity agent, and as a vehicle (bulking agent) for lyophilized preparations. It was provided from (Roquette, lestrem, France).



Disintegrant

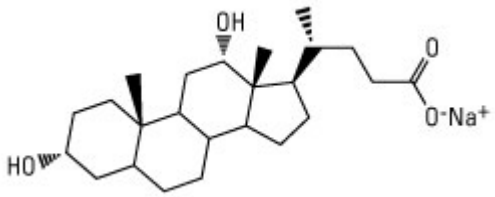
Primojel is DFE Pharma's product brand name for sodium starch glycolate (type A). Primojel® complies with the requirements of the Ph. Eur., USP-NF and JP monographs. Primojel® is made in a dedicated pharmaceutical plant in Foxhol, the Netherlands.

Primojel® is chemically cross-linked and carboxymethylated potato starch. It is manufactured by cross-linking starch with sodium trimetaphosphate followed by carboxymethylation with sodium monochloroacetate. Approximately one glucose monomer unit in every four is substituted. It was provided from (DMV international, Veghel, The Netherlands).



Surfactants

Sodium deoxycholate (SDC) contains both hydrophobic groups (their *tails*) and hydrophilic groups. The insoluble hydrophobic group may extend out of the bulk water phase, into the air or into the oil phase, while the water soluble head group remains in the water phase. This alignment of surfactant molecules at the surface modifies the surface properties of water at the water/air or water/oil interface. It was provided from (Sigma, Aldrich Chemie GmbH, Stein heim, Germany).



Sodium Lauryl Sulfate is a salt of an organosulfate consisting of a 12-carbon tail attached to a sulfate group, giving the material the amphiphilic properties required for a detergent. It was provided from (BUFA B.V. Uitgeest, The Netherlands)

4.2.2 PROCEDURES & APPARATUS

4.2.2.1 Determination of solubility

Solubilities of Amphotericine B in demineralized water and in acidic solution (*pH*=1.2) were determined by means of the Shake-Flask method [22]. Suspensions of Amphotericine B in presence of carrier and one of the studied surfactants (SDC or SLS) in closed vessels were stirred at 37°C for 3 days and were then filtered with a 0.2 μm filter prior to analysis. The filtrate was diluted, if necessary, and analyzed by UV-Spectrophotometry at wavelength of 333 and 337 nm for Amphotericine B in acidic (*pH*=1.2) and aqueous solutions, respectively. All measurements were performed in triplicate.

4.2.2.2 Preparation of physical mixtures (PM)

Physical mixtures composed of crystalline drug (as received) and lyophilized carriers and surfactants in the case of using them in the corresponding ratios of solid dispersions were prepared by gently mixing using a mortar and a spatula. The samples were placed in a vacuum desicator over silica gel at room temperature for at least one day before use.

4.2.2.3 Preparation of solid dispersions (SD)

The method used in this work to prepare solid dispersions, was freeze drying method, also known as lyophilization. The solid dispersions were prepared as follows: Drug-carriers (inulin and mannitol) and the drug (Amphotericine B) and in the case of having surfactants (SLS and SLD) were dissolved all together in dimethyl sulfoxide (DMSO). The obtained solutions were pipetted into 10-mL vials (1 mL in each vial). Subsequently, the solution was frozen in liquid nitrogen and lyophilized. In a typical lyophilization cycle the frozen solution was placed on the shelf of a Christ model Alpha 2-4 lyophilizer (Salm and Kipp, Breukelen, The Netherlands) shown in Fig. 4.2.1. Lyophilization was performed according to a two-step procedure. First, the pressure was set at 0.220 mbar and the shelf temperature at -35°C for one day. Subsequently, the pressure was reduced to 0.05 mbar, while the shelf temperature was

gradually raised to 5°C. This condition was maintained for another day. During the whole cycle the condenser temperature was constant. After freeze drying the samples were placed in a vacuum desiccator over silica gel at room temperature for at least one day. An overview of the prepared solid dispersions is given in Table 4.2.1.

Figure 4.2.1: Christ model Alpha 2-4 lyophilizer

Table 4.2.1: Preparation of solid dispersions

Drug (type)	Drug load (%)	Carrier (type)	Carrier load (%)	Disintegrant (type)	Disintegrant load (%)	Surfactant (type)	Surfactant load (%)
AmB	25	Mannitol	75	-	-	-	-
AmB	25	Mannitol	71	Primojel	4	-	-
AmB	25	Inulin	75	-	-	-	-
AmB	25	Inulin	71	Primojel	4	-	-
AmB	6	Mannitol	94	-	-	-	-
AmB	6	Mannitol	88	-	-	SLS	6
AmB	6	Mannitol	82	-	-	SLS	12
AmB	6	Mannitol	88	-	-	SDC	6
AmB	6	Mannitol	82	-	-	SDC	12

AmB: Amphotericine B

4.2.2.4 Tabletting

The die of the tableting machine (Hydro Mooi, Appingedam, Netherlands) shown in Fig. 4.2.2 was filled with 50, 100 and 200 mg solid dispersion or physical mixture without other excipients. The die was lubricated with magnesium stearate. The samples were compressed to round and flat tablets using an ESH compaction apparatus equipped with a punch-die set with a diameter of 7 mm. The maximum force of 5 kN was reached in 1 s. The compositions of tablets are shown in Table 4.2.1. The tablets were stored for at least one day in a vacuum desiccator over silica gel at room temperature and in the other way at temperature of 4°C before analysis.

Figure 4.2.2: Tableting machine

4.2.2.5 X-Ray Powder Diffraction (XRPD)

Samples were analyzed using an X'Pert PRO MPD diffractometer (PANalytical, Almelo, The Netherlands) with a copper anode (Cu Kα radiation, λ= 0.15405 nm, 40 kV, 40 mA) shown in Fig. 4.2.3. Samples were scanned from 4 to 60° 2θ with a step size of 0.008° and a time per step of 45 s at ambient temperature. The powders were placed on a zero-background silicon holder of 32 mm in diameter and 2 mm thickness.

Figure 4.2.3: X'Pert PRO MPD diffractometer

4.2.2.6 Dissolution of tablets

Dissolution of tablets was performed by using a USP dissolution apparatus II (Rowa Techniek, Leiderdorp, Netherlands) with a paddle at 100 rpm and 37°C shown in Fig. 4.2.4. The dissolution medium was continuously circulated through UV-spectrophotometer flow cells (Model Ultraspec III; Pharmacia LKB, Uppsala, Sweden) at 20 mL/min using a peristaltic pump (Ismatec, Zurich, Switzerland). The samples were filtered through 0.35 µm filters prior to analysis. Concentrations of Amphotericine B in the dissolution medium were measured every 2 min over a two-hour period at a wavelength of 333 and 337 nm in acidic (*pH*=1.2) and aqueous (demineralized water) medium (900 mL) respectively. In a number of cases, 1.0 mL samples were taken at different time intervals. Subsequently, the concentration of sample was determined using UV-Spectrophotometry at wavelength of 333 and 337 nm for Amphotericine B in acidic (*pH*=1.2) and aqueous solutions, respectively. Calibration curve of 10, 20, 30, 40 and 50 mg/mL of Amphotericine B at a wavelength of 333 and 337 nm were obtained by UV-Spectroscopy instrument. Measurements were performed in triplicate. The standard deviation was considered less than 5. All experiments were done in two different ways:

a. Experiments were done without any protection from light and after making solid dispersion were kept in the room temperature.

b. Experiments were done in complete protection from light and after making solid dispersion were kept in the fridge with temperature of 4°C.

Figure 4.2.4: USP dissolution apparatus I

4.3 RESULTS & DISCUSSION

4.3.1 Solubility study

As can be seen in Table 4.3.1, the solubility of Amphotericine B in demineralized water in presence of mannitol is in complete agreement with the one from literature [24]. It also shows the irrelevance of carrier presence on the solubility of the drug. Morever, the measured solubility with or without surfactant added was not significantly different. This indicates that surafctants (SLS and SDC) in the applied concentration of 6 or 12% w/w did not affect the aqueous solubility of the drug. The saturation concentration of Amphotericine B in demineralized water was 33.61±1.7 mg/L. Compared to the solubility of Amphotericine B in demineralized water, the solubility of the drug in the acidic solutions was strongly increased, about 2 times more than the one obtained in demineralized water. In the cited work it has been found that the solubility of Amphotericine B increased in acidic solutions [24].

Table 4.3.1: Solubility of Amphotericine B in solid dispersion in demineralized water and in acidic (*pH*=1.2) ambient including the carrier and 6 or 12 % w/w of surfactants (SLS and SDC), 37°C (n=3)

	Aqueous ambient, λ=337nm					**Acidic ambient (*pH*=1.2), λ =333nm**				
Solid composition										
Amphotericine B (% w/w)	6	6	6	6	6	6	6	6	6	6
Mannitol (% w/w)	94	88	82	88	82	94	88	82	88	82
SDC (%w/w)	-	6	12	-	-	-	6	12	-	-
SLS (% w/w)	-	-	-	6	12	-	-	-	6	12
Solubility of Amphotericine B (mg/L)	33.61	32.21	32.86	33.25	32.9	72.27	72.35	72.46	70.95	71.81

Preliminary measurements using inulin as the carrier lead to a similar conclusion.

4.3.2 XRPD studies

Fig. 4.3.1A shows that pure Amphotericine B exhibited the XRPD pattern with sharp peaks which show its crystallinity. In Fig. 4.3.1B, mannitol also exhibited the XRPD pattern with also sharp peaks according to its crystalline form. In Fig. 4.3.1C, XRPD patterns of mannitol-based solid dispersions with Amphotericine B incorporated showed no distinctive peaks of crystalline Amphotericine B justifying that the drug is present in amorphous form. However, In Fig. 4.3.1D, the physical mixture of the same composition exhibited sharp peaks related to both mannitol and Amphotericine B and show the presence of the crystalline form of the drug. These features can be clearly observed in the overlapped graphs given in Fig. 4.3.2. Fig. 4.3.2A shows the XRPD patterns of mannitol together with the one of solid dispersion of 6% w/w Amphotericine B in mannitol and perfect concordance can be seen between black graph corresponding to the mannitol and red graph corresponding to the solid dispersion of 6% w/w Amphotericine B in mannitol. However, Fig. 4.3.2B shows the XRPD of Amphotericine B together with the one of solid dispersion of 6% w/w Amphotericine B in mannitol and there is not a good fitness between black graph corresponding to Amphotericine B and red graph corresponding to the solid dispersion. This clearly indicated that sharp peaks of solid dispersion shown in Fig. 4.3.1C correspond to the crystallinity of mannitol but not to the Amphotericine B. Therefore, it is concluded that 6% w/w Amphotericine B incorporated in mannitol as solid dispersion was fully amorphous.

In the case that inulin was used as carrier, XRPD patterns of all solid dispersions in which Amphotericine B was incorporated, confirmed that the drug is fully amorphous too. In Fig. 4.3.3B, Inulin presented a broad diffraction pattern indicating its amorphous state. In Fig. 4.3.3C, the solid dispersion of 25% w/w Amphotericine B in inulin showed also a broad diffraction peak and lack of the typical sharp peaks of crystalline Amphotericine B.

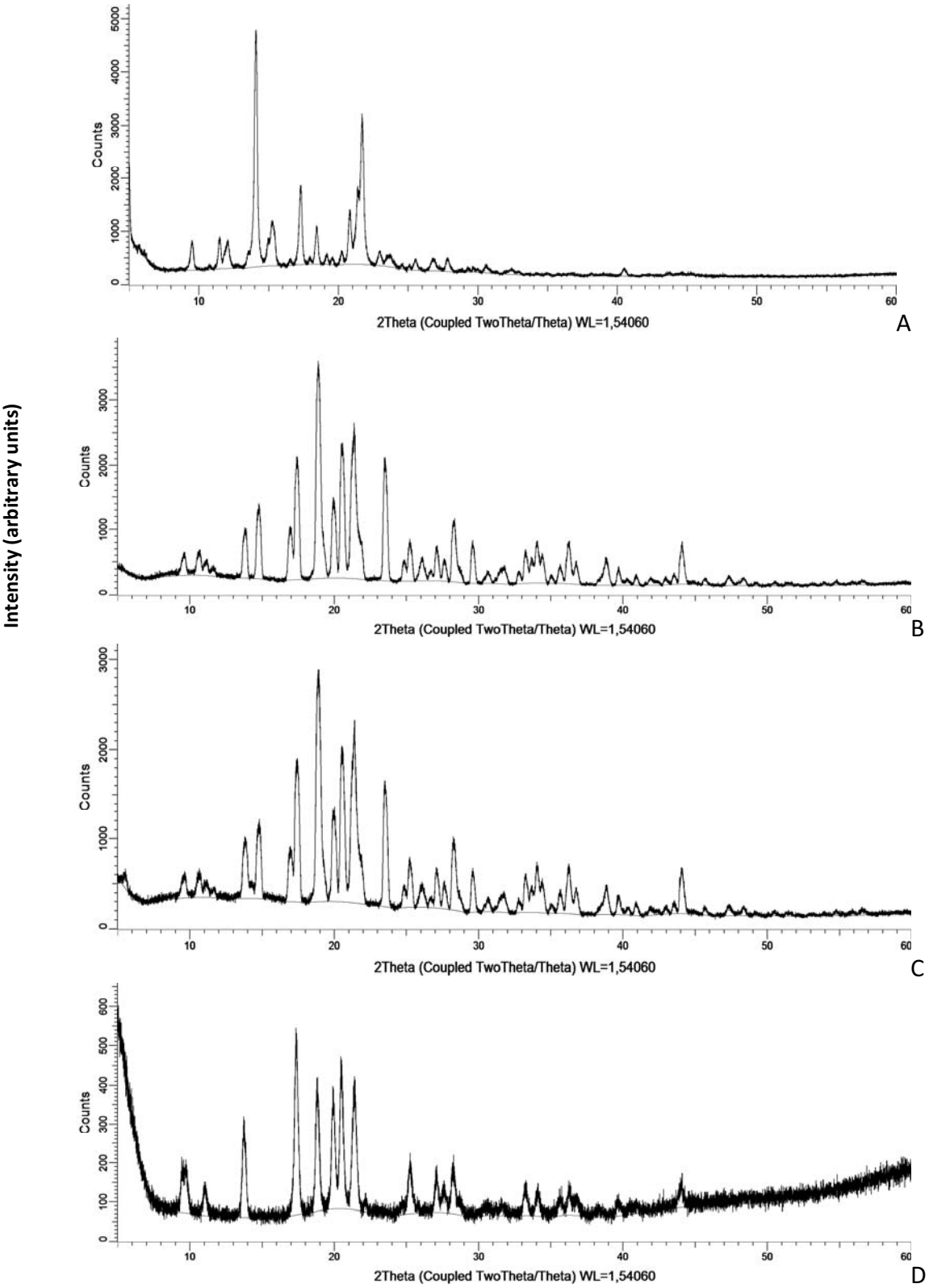


Figure 4.3.1: XRPD patterns of (A) Crystalline Amphotericine B (B) Mannitol, and (C) Solid dispersion of 6% w/w Amphotericine B in Mannitol, (D) Physical mixture of 6% w/w Amphotericine B in Mannitol

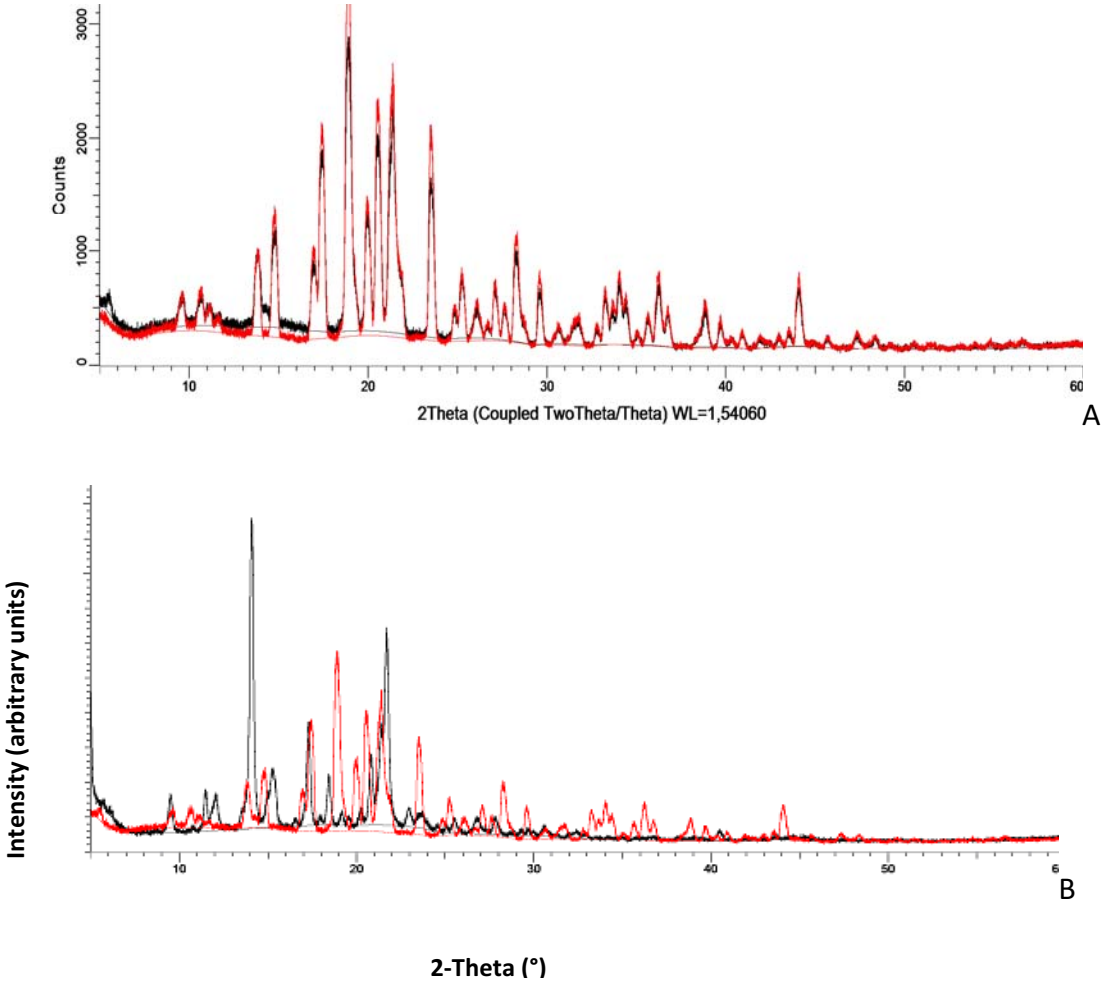


Figure 4.3.2: XRPD patterns of (A) mannitol together with the one of solid dispersion of 6% w/w Amphotericine B in mannitol (B) Amphotericine B together with the one of solid dispersion of 6% w/w Amphotericine B in mannitol.
Black graph in A: Mannitol
Black graph in B: Amphotericine B
Red graph: Solid dispersion of 6% w/w Amphotericine B in mannitol

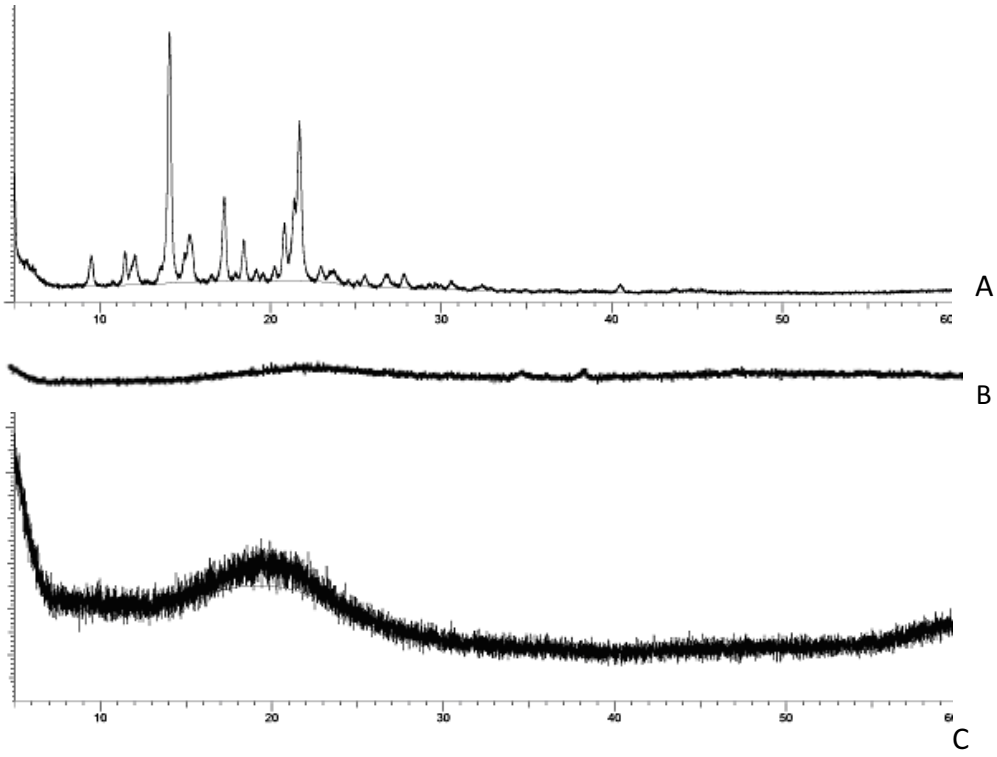


Figure 4.3.3: XRPD patterns of (A) Crystalline Amphotericine B (B) Inulin, and (C) solid dispersion of 25% w/w Amphotericine B in inulin.

4.3.3 Dissolution studies

4.3.3.1 Tablets prepared from physical mixtures or solid dispersions of Amphotericine B in mannitol or inulin

The dissolution behaviour of tablets prepared from inulin or mannitol-based physical mixtures or solid dispersions and at a drug load of 25% w/w was evaluated in acidic (*pH*=1.2) medium. Tablets were prepared in two different ways, with primojel as a disintegrant or without it. In these experiments, the concentrations of Amphotericine B released from these tablets were determined. All measurements were done triple and the standard deviation was less than 5 mg/L.

The dissolution profiles of inulin or mannitol-based tablets are shown in Fig. 4.3.4 and Fig. 4.3.5. In Fig. 4.3.4, for physical mixture tablets with and without primojel, Amphotericine

B was dissolved, very slowly and after 2 hours, only about 5 and 4% of the drug, respectively is in solution but about 10 and 6% of the drug was dissolved from tablets prepared with solid dispersions. As it was expected, the dissolution of solid dispersion and physical mixture tablets with primojel was faster than that without primojel, but the difference was really small. These results can be ascribed to the fact that during dissolution, the solid dispersion with primojel tablets disintegrated while those without primojel gradually eroded which was visually observed.

The dissolution profiles of mannitol-based tablets are presented in Fig. 4.3.5 for tablets prepared from physical mixtures with and without primojel. Amphotericine B was dissolved very slowly and after 2 hours, only about 5 and 4% of the drug respectively were in solution. On the other hand, Amphotericine B incorporated in tablets prepared from solid dispersion with primojel and without primojel also dissolved slowly and after 2 hours, only about 12.5 and 7% of the drug was dissolved. As it was expected, the dissolution of solid dispersion and physical mixture tablets with primojel was faster than those without primojel. In fact, the dissolution behaviour is very similar to that of the inulin-based tablets and in both instances, the solid dispersion with primojel tablets disintegrated while those without primojel gradually eroded.

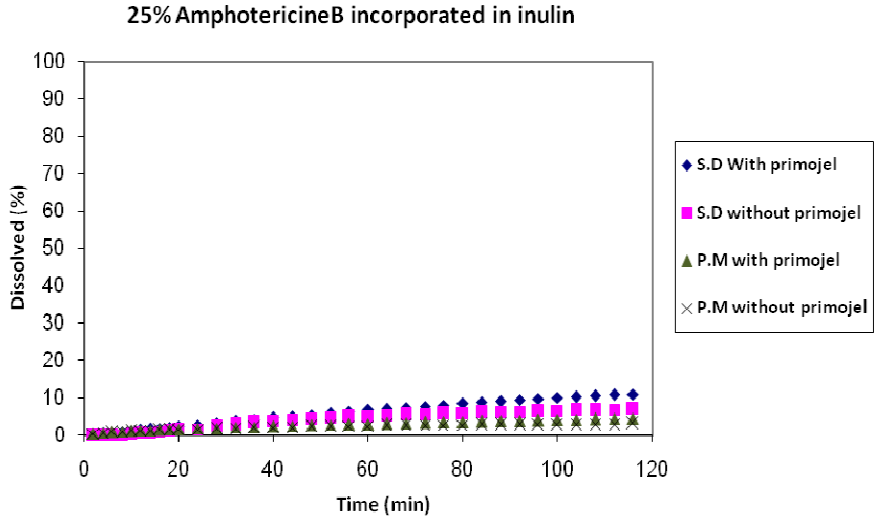


Figure 4.3.4: Dissolution profile of physical mixtures (PM) and solid dispersions (SD) with and without primojel

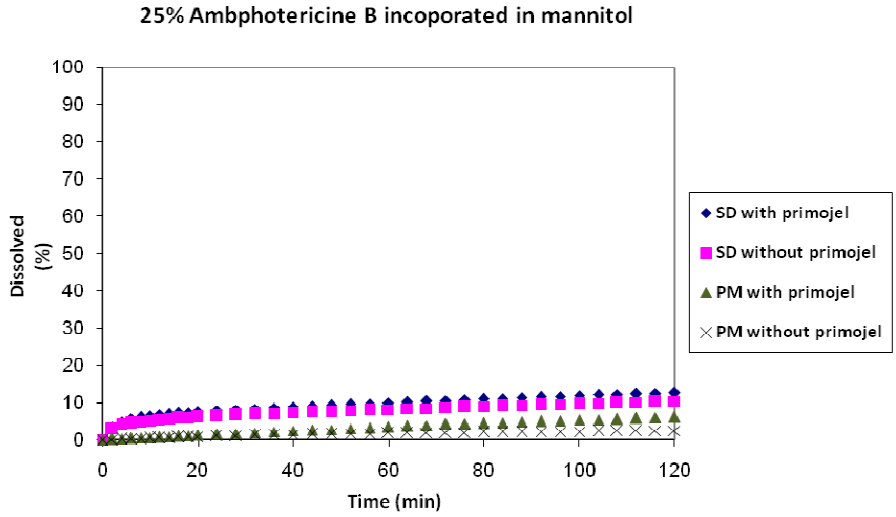


Figure 4.3.5: Dissolution profile of physical mixtures (PM) and solid dispersions (SD) with and without primojel

In both inulin and mannitol-based and solid dispersion tablets, dissolution rate is about two times more than those from the physical mixture tablets but still the values are considered very low. In all cases also with primojel show slightly higher dissolution rate than those without primojel. We supposed that there are not enough porous in tablets and the disintegrant can not act properly. In any case, the effect of the presence of primojel is very small. Mannitol seems to be the better carrier in comparision with inulin because of slightly higher dissolution rate observed in the results and also it disintegrate faster and inhibits drug to recrystalize. That is why we decided to choose mannitol as the carrier in the rest of the experiments. Moreover, the concentration of Amphotericine B was decreased from 25% to 6% in the tablets.

4.3.3.2 Tablets prepared from physical mixtures or solid dispersions of Amphotericine B in mannitol with SDC

The dissolution behavior of tablets prepared from mannitol-based physical mixtures and solid dispersions at a drug load of 6% w/w with different amount of SDC (0, 6 and 12%) were evaluated in both acidic (*pH*=1.2) and aqueous dissolutions.

In this instance, surfactants were used to reduce the surface tension of solution to help drug to be dispersed in water and hence get solubilized. SDC surfactant is soluble in aqueous solution, but little soluble in acidic ambient. In these experiments, the concentrations of Amphotericine B released from these tablets were determined.

The dissolution profiles of mannitol-based tablets with different amount of SDC in acidic solution (*pH*=1.2) are shown in Fig. 4.3.6. Fig. 4.3.6 A, B, C (using 0%, 6% and 12% of SDC surfactant, respectively) shows that in all physical mixture tablets, Amphotericine B was dissolved, as expected, very slowly and after 20 minutes, only about 10%, 5% and 5% of the drug, respectively, is in the solution. As it was expected, Amphotericine B incorporated in solid dispersion tablets dissolved faster in all cases in comparision with physical mixture tablets and after 20 minutes, about 20%, 50% and 10% of the drug was dissolved respectively. Whereas the dissolution rate for physical mixture tablet is practically unaffected by the presence of surfactant, its effect is notorious for solid dispersion tablets at moderate concentration of SDC (about 6%). Larger concentrations of surfactant reduce its effect on the dissolution rate. In all instances, a constant concentration value is achieved in the solution in about 30 minutes.

The dissolution profiles of mannitol-based tablets with different amount of SDC surfactants in aqueous dissolution are shown in Fig. 4.3.7. Even here, in all cases, the disolution of solid dispersion tablets was faster than those prepared from physical mixtures and the difference in all cases were considerable. Moreover, the higher the amount of added SDC, the higher the dissolution rate for both kinds of tablets examined here.

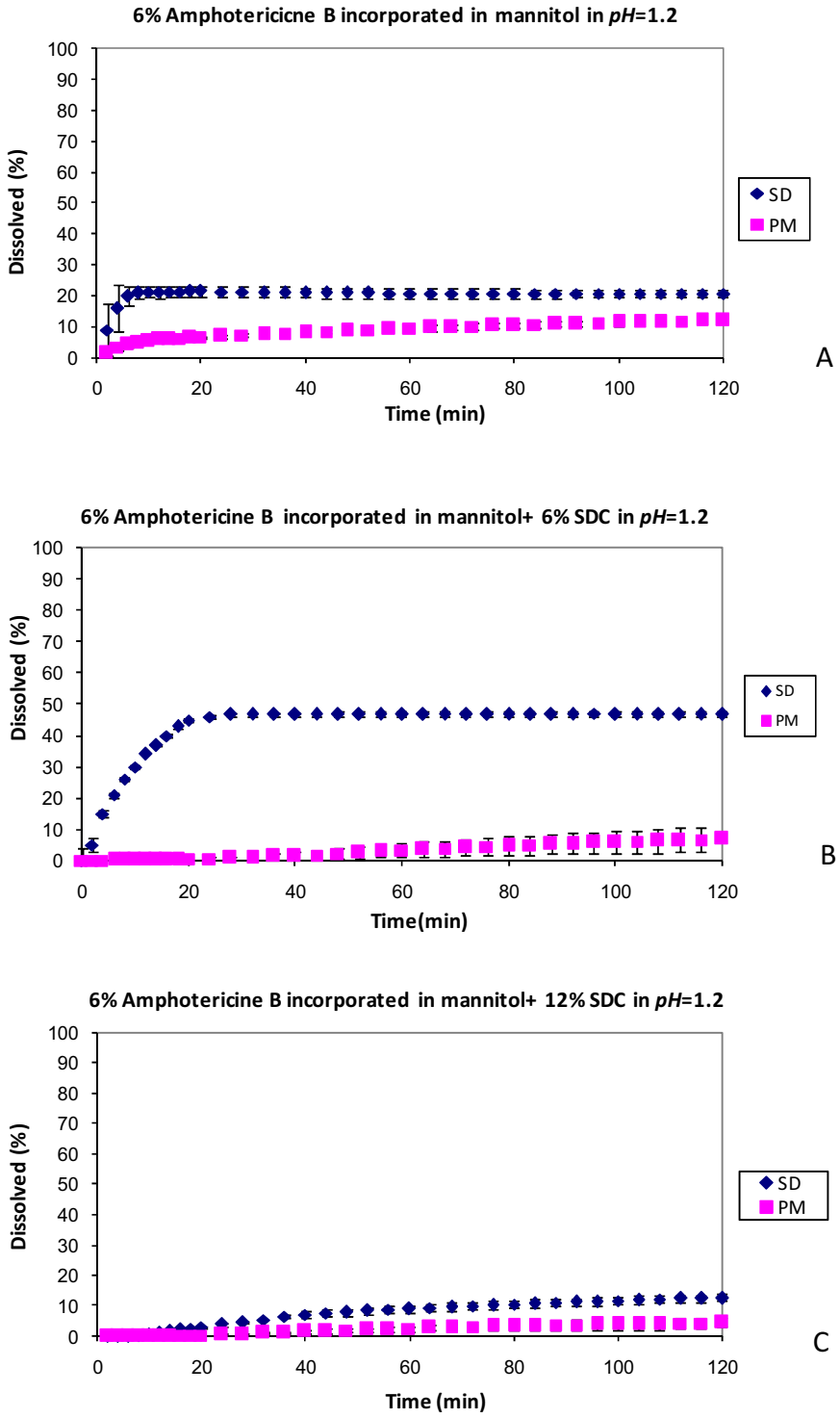


Figure 4.3.6 : Dissolution profile of physical mixtures and solid dispersions of 6% w/w Amphotericine B with 0% (A) , 6% (B) & 12% (C) of SDC surfactant in mannitol in acidic (*pH*=1.2) dissolution.

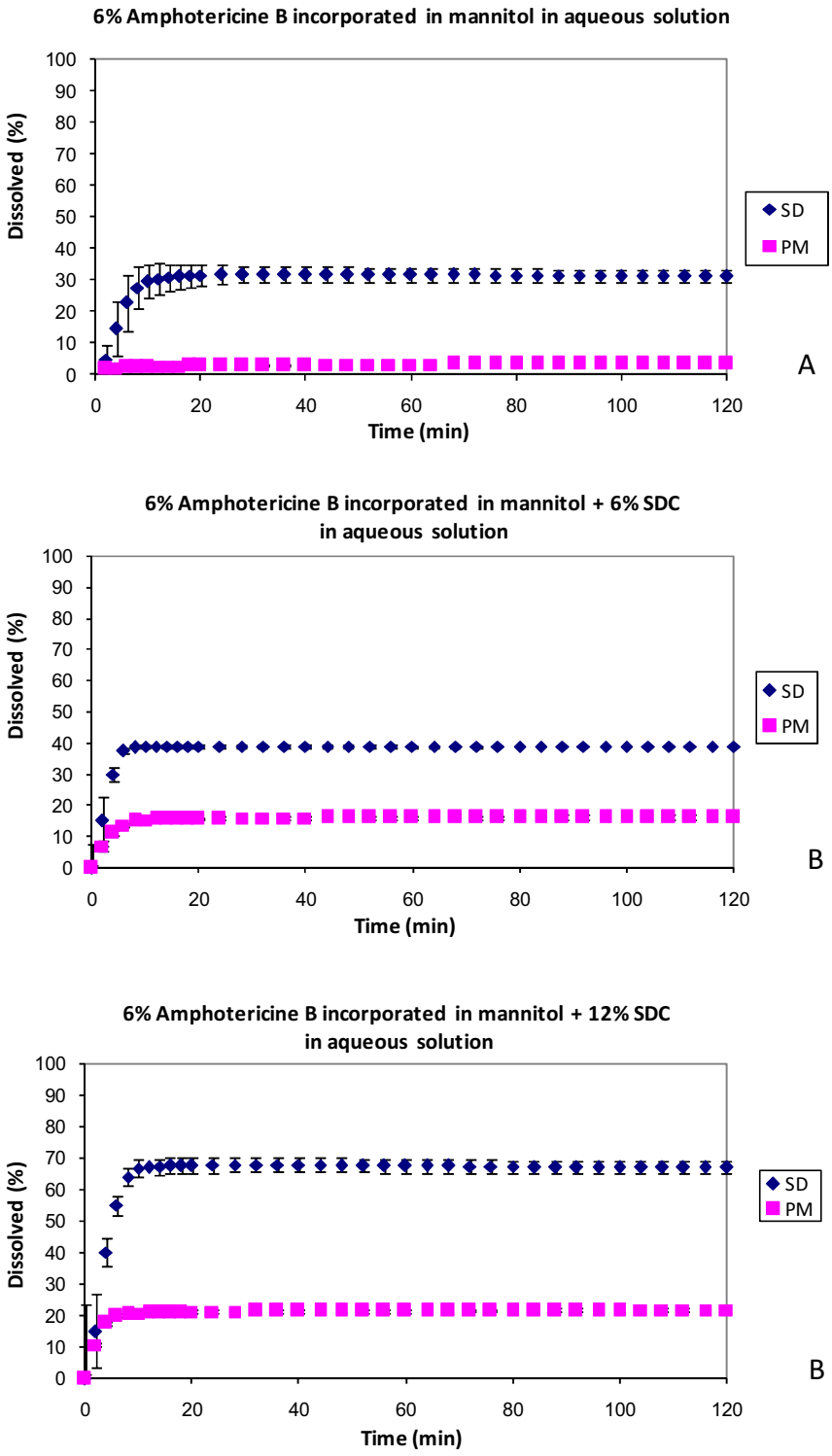


Figure 4.3.7: Dissolution profile of physical mixtures and solid dispersions of 6% w/w Amphotericine B with 0% (A), 6% (B) & 12% (C) of SDC surfactant in mannitol in aqueous dissolution.

4.3.3.3 Tablets prepared from physical mixtures or solid dispersions of Amphotericine B in mannitol with SLS

The dissolution behavior of tablets prepared from mannitol-based physical mixtures and solid dispersions at a drug load of 6% w/w with different amount of SLS (0, 6 and 12%) were evaluated in both acidic (*pH*=1.2) and aqueous dissolution. In these experiments, the concentrations of Amphotericine B released from these tablets were determined.

The dissolution profiles of mannitol-based tablets with different amount of SLS surfactant in acidic (*pH*=1.2) dissolution are shown in Fig. 4.3.8. Fig. 4.3.6 A, B, C (0%, 6% and 12% of SLS surfactant, respectively) shows that, Amphotericine B incorporated in solid dispersion tablets dissolved slowly and after 20 minutes, about 22%, 40% and 16% of the drug respectively was dissolved. The higher dissolution rate of Amphotericine B corresponds to the solid dispersion tablets including 6% SLS surfactant. The same dissolution rate behavior was seen in the case that SDC surfactant was used in acidic dissolutions.

The dissolution profiles of mannitol-based tablets with different amount of SLS surfactant in aqueous dissolution are shown in Fig. 4.3.9. Fig. 4.3.9 A, B, C (0%, 6% and 12% of SLS surfactant, respectively) shows that Amphotericine B incorporated in solid dispersion tablets dissolved after 20 minutes, about 30%, 42% and 45%, respectively. It was observed that, the increase of SLS surfactant amount from 6 to 12% has no significant effect on desintegration and dissolution rate of solid dispersion. This behaviour clearly differs from that observed when SDC was used.

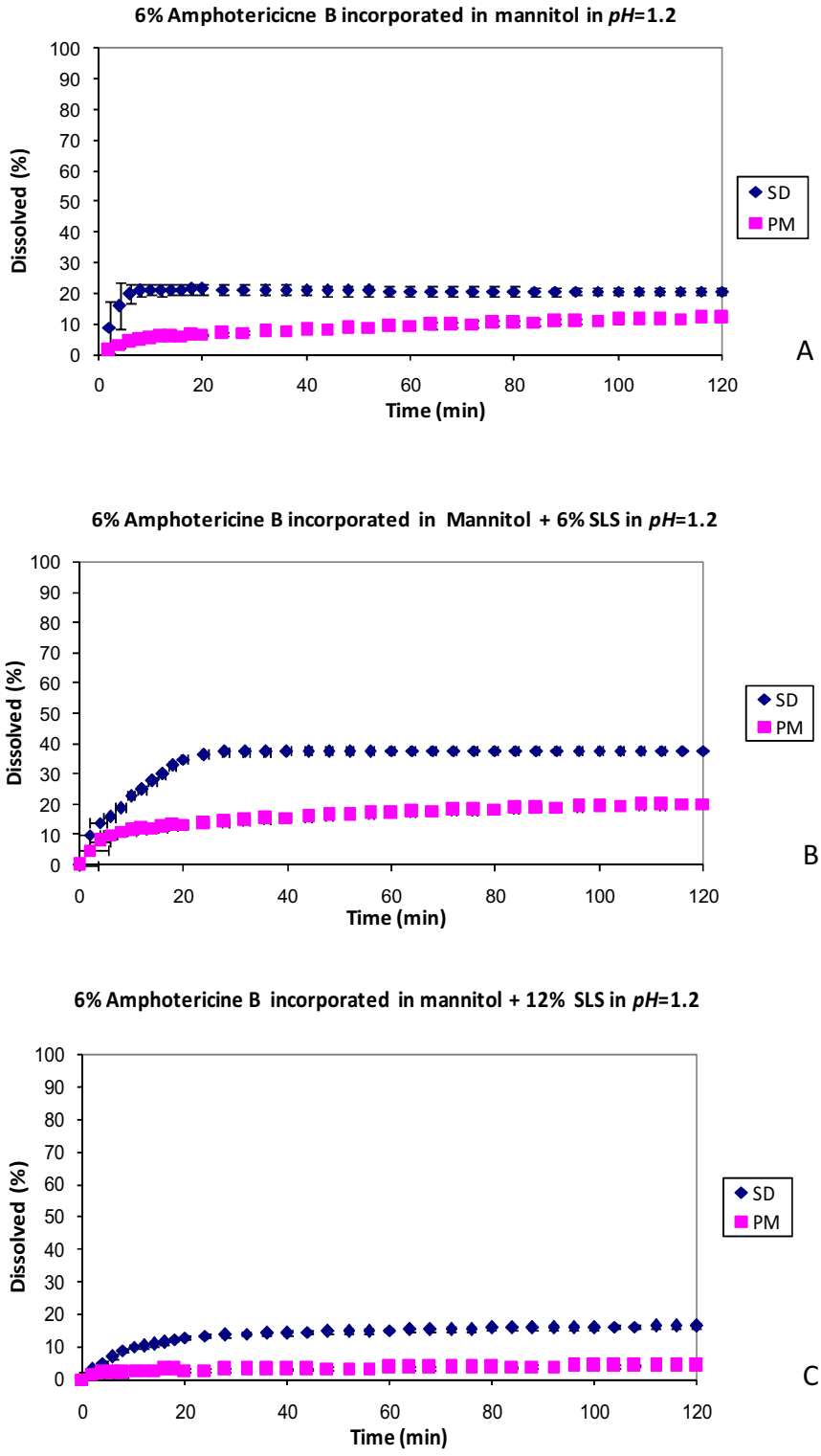


Figure 4.3.8: Dissolution profile of physical mixtures and solid dispersions of 6% w/w Amphotericine B with 0%, 6% & 12% of SLS surfactant in mannitol in acidic (*pH*=1.2) dissolution.

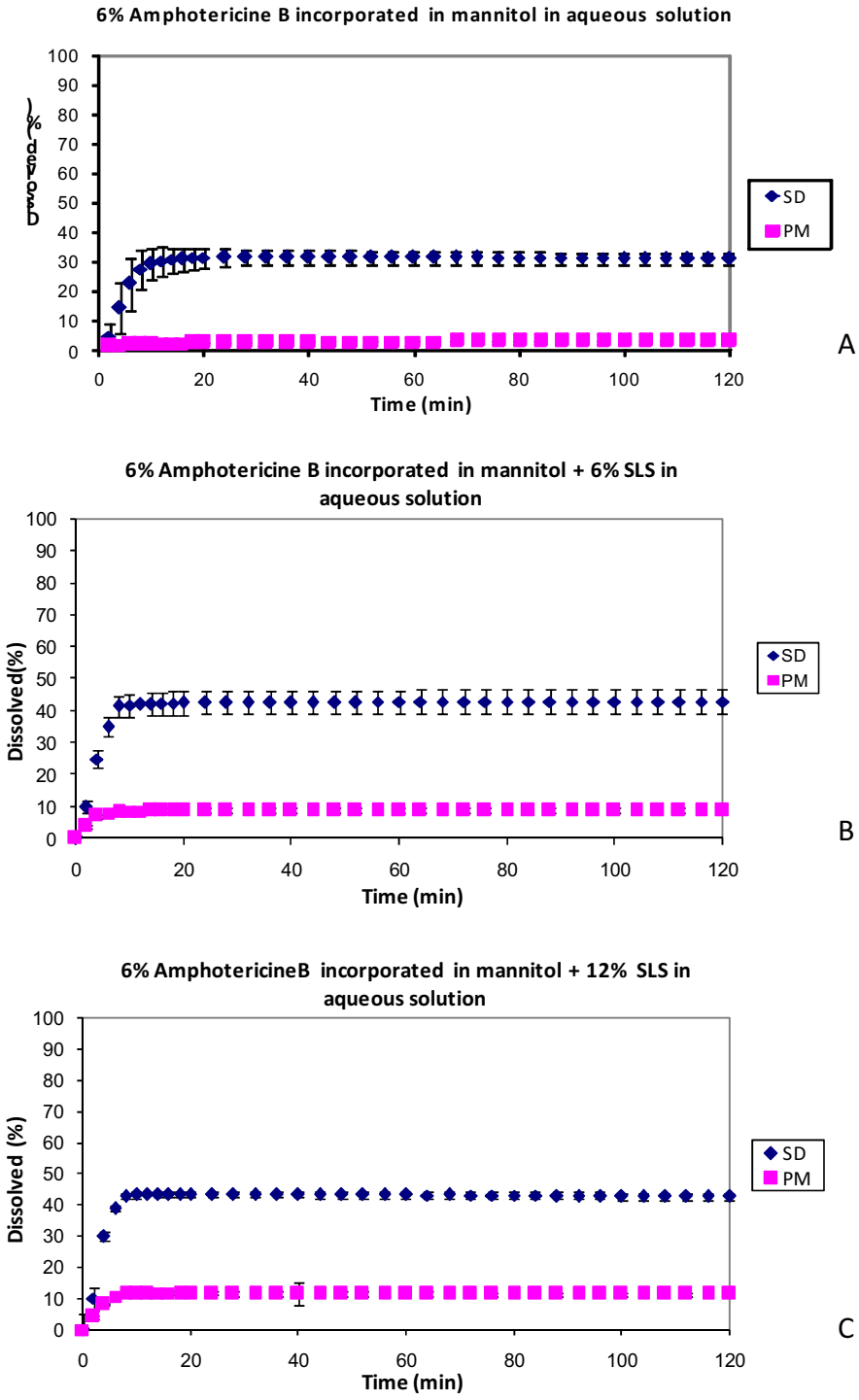


Figure 4.3.9: Dissolution profile of physical mixtures and solid dispersions of 6% w/w Amphotericine B with 0% (A), 6% (B) & 12% (C) of SLS surfactant in mannitol in aqueous dissolution.

4.3.3.4 Comparision of dissolution behaviour of solid dispersions of Amphotericine B in mannitol with SDC & SLS

The results obtained clearly show that dissolution rate of tablets prepared from solid dispersions are higher than those from physical mixtures in all cases, independently of the nature of added surfactant.

The dissolution behaviour of tablets prepared from mannitol-based solid dispersions a drug load of 6% w/w with different amount of SLS (0,6 and 12%) in aqueous and acidic media were compared with those from tablets with the same doses of drug but with different amounts of SDC (0,6 and 12%) in the same ambients. The difference between the effect of both surfactants in aqueous and acidic media on the dissolution rate is remarkable only for aqueous solutions and 12% w/w of surfactant as shown in Table 4.3.2. This table summarizes also a similar behaviour in acidic medium in presence of SLS or SDC, with a maximum value in the dissolution rate in tablets prepared with a 6% of surfactant.

In summary, the best dissolution rate is achieved in aqueous solution for tablets prepared from solid dispersions with mannitol as the carrier and SDC as the added surfactant. Nevertheless, the dissolution of the drug under these conditions is not enough to be considered satisfactory and lot of work should be done to get a more complete drug release.

Table 4.3.2: Dissolved (%) Amphotericine B in acidic (*pH*=1.2) and aqueous dissolution, including 0, 6 and 12 % w/w of surfactants (SLS and SDC), 37°C (n=3)

	SDC		SLS	
Surfactant	**Aqueous**	***pH*=1.2**	**Aqueous**	***pH*=1.2**
0	30	20	30	22
6	40	50	42	40
12	70	10	45	16

4.3.3.5 Effect of protective and unprotective way from light on dissolution rate of mannitol- based solid dispersion tablets

The effect of light on the dissolution rate of tablets prepared from mannitol-based solid dispersions and physical mixtures at a drug load of 6% w/w of Amphotericine B were studied for a representative sample, just for tablets with different amount of SLS (0,6 and 12%) in acidic (*pH*=1.2) dissolution by protecting the system from light in all processes. In these experiments, the concentrations of Amphotericine B released from these tablets were determined.

The dissolution profiles of tablets with different amount of SLS surfactants in acidic (*pH*=1.2) dissolution are shown in Fig. 4.3.10. Fig. 4.3.10 A, B, C (0%, 6% and 12% of SLS surfactant, respectively) shows that, Amphotericine B incorporated in solid dispersion tablets dissolved about 40%, 60% and 30% respectively, after 20 minutes. Thus, dissolution rate has been significantly increased from 22%, 40% and 16% (Fig. 4.3.8 A, B, C) by protecting the system from light, but still it is considered low. Even here, in solid dispersions including SLS surfactant in acidic dissolution (*pH*=1.2), the effect of SLS surfactant seems to be higher at moderate SLS surfactant concentration. In addition, it has been observed that the protective procedure improved a little the dissolution behaviour in drug even in samples without surfactant.

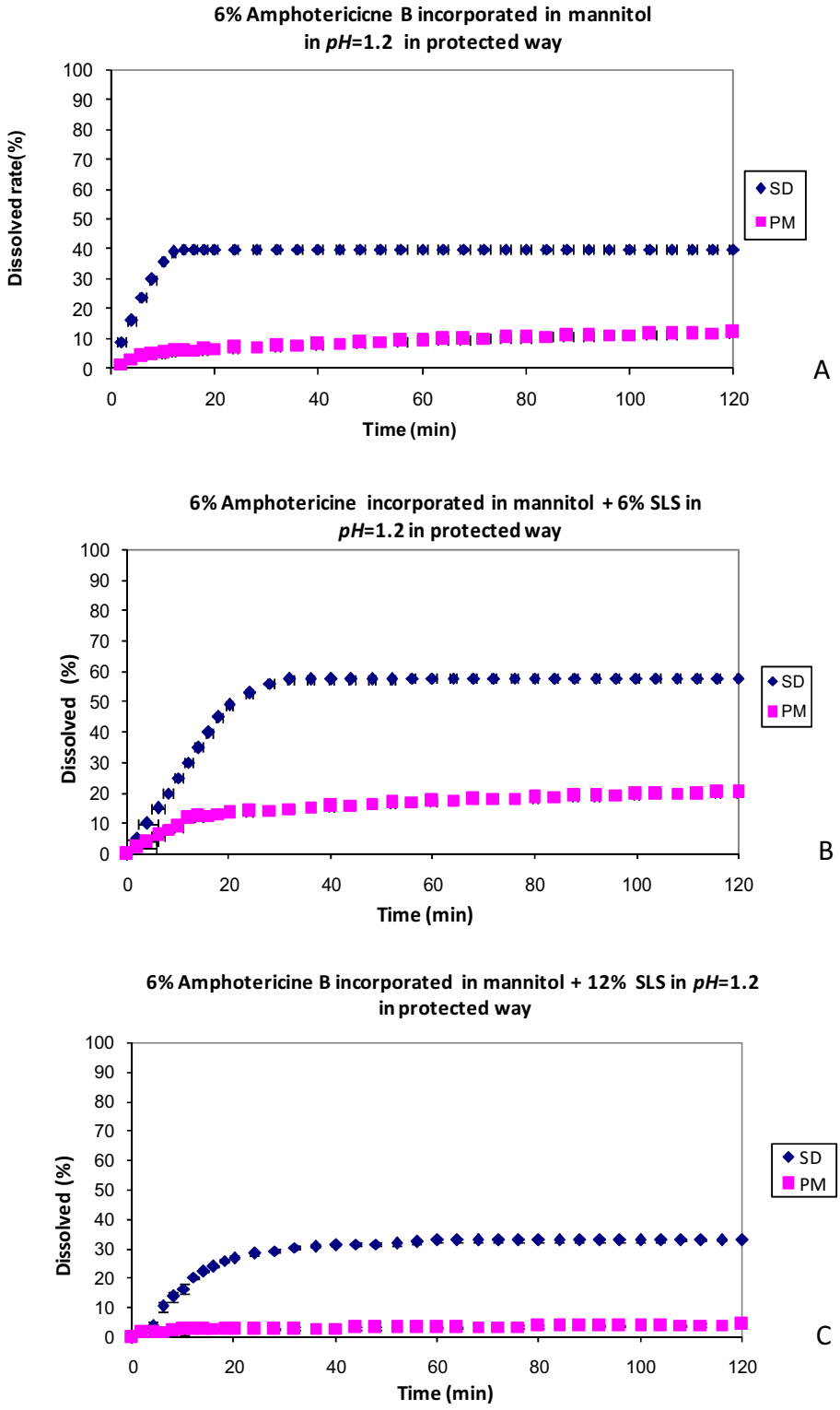


Figure 4.3.10: Dissolution profile of physical mixures and solid dispersions of 6% w/w Amphotericine B with 0% (A), 6% (B) & 12% (C) of SLS surfactant in mannitol in acidic (*pH*=1.2) dissolution.

In short, a promising way to increase the bioavailability of Amphotericine B is the increase its dissolution rate by means of the preparation solid dispersions of the drug by means of the freeze drying method. This study involves the examination of the solution behaviour of solid dispersions prepared in different ways: with and without drug-carrier and also with and without surfactants. It was found that the drug dissolution rate in aqueous and acidic solutions was significantly increased in the presence of drug-carrier and surfactants. X-ray powder diffraction revealed that all solid dispersions were fully amorphous. The dissolution behaviour of tablets prepared from mannitol-based solid dispersions a drug load of 6% w/w with different amount of SLS (0,6 and 12%) in aqueous and acidic media were compared with those from tablets with the same doses of drug but with different amounts of SDC (0,6 and 12%) in the same ambients. The difference between the effect of both surfactants in aqueous and acidic media on the dissolution rate is remarkable only for aqueous solutions and 12% w/w of surfactant, being SDC the more efficient surfactant. In summary, the best dissolution rate is achieved in aqueous solution for tablets prepared from solid dispersions with mannitol as the carrier and SDC as the added surfactant. Nevertheless, the dissolution of the drug under these conditions is not enough to be considered satisfactory and lot of work should be done to get a more complete drug release.

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Conclusiones

CONCLUSIONES

La presente tesis se ha centrado en el estudio de dos características físico-químicas muy significativas de las sustancias orgánicas bioactivas, la acidez y la solubilidad. Las conclusiones alcanzadas se resumen a continuación:

1) Determinación potenciométrica del pK_a de sustancias orgánicas en solución acuosa y en algunas mezclas de metanol y agua a varias temperaturas.

Con el objetivo de verificar y ampliar la metodología potenciométrica propuesta por Sirius Analytical Ltd. para la determinación de las constantes de acidez termodinámicas en agua pura y en diversas mezclas metanol/agua en un intervalo amplio de temperatura, se han seleccionado la anilina y el tris (hidroximetil)-aminometano (tris) como prototipos de bases y los ácidos benzoico y acético para estudiar el comportamiento de los ácidos. Se han determinado los cuatro parámetros de estandarización del sistema potenciométrico (α_o, S_o, j_{oH} y j_{oOH}) en solución acuosa y a 25°C y se han calculado los correspondientes valores para cada mezcla metanol/agua en estudio y a cualquier temperatura de interés en el intervalo 25-55°C (α, S, j_H and j_{OH}). Se han calculado también las constantes dieléctricas de las mezclas de metanol/agua de interés (0-60% w/w) en el intervalo de temperatura de 25-55°C y los parámetros de la ecuación de Debye-Hückel (A y a_0B) en las condiciones de trabajo. El procedimiento utilizado ha llevado a resultados que demuestran claramente que éste se puede aplicar para obtener valores precisos de las constantes de acidez en agua pura y en las mezclas hidroorgánicas e intervalo de temperatura en estudio.

Los valores de ${}^{s}_{s}pK_a$ del anilinio, tris protonado, ácido benzoico y ácido acético en las diferentes mezclas metanol/agua (0-60% w/w) y a distintas temperaturas (25-55°C) han permitido calcular los coeficientes de las correspondientes ecuaciones de Yasuda-Shedlovsky, las cuales permiten la interpolación de valores de ${}^{s}_{s}pK_a$. A partir de estos valores interpolados se han calculado las variaciones de entalpía de

los procesos de disociación ácida (ΔH) mediante la ecuación de Van't Hoff. Los valores de ΔH calculados son concordantes con los de la literatura, determinados directamente por calorimetría para el agua pura y para mezclas de metanol/agua 50% w/w.

En consecuencia, se concluye que el procedimiento de estandarización del sistema potenciométrico propuesto es adecuado en un amplio intervalo de composición del disolvente (metanol/agua, 0-60% w/w) y de temperatura (25-55^{o}C) y lleva a valores correctos de ${}^{s}_{s}pK_a$ los cuales permiten, a su vez, el cálculo de las entalpías de disociación ácida. La verificación de la bondad de los resultados obtenidos se ha hecho por comparación con los valores obtenidos por técnicas independientes que ofrece la literatura.

2) Determinación potenciométrica de la solubilidad de sustancias orgánicas bioactivas en solución acuosa

Con los objetivos de verificar y de determinar las condiciones óptimas de trabajo en la metodología potenciométrica propuesta por Sirius Analytical Ltd. para la determinación de la solubilidad de compuestos orgánicos, se ha examinado la solubilidad de una base de referencia, la lidocaína, y una serie de compuestos básicos homólogos, ésteres derivados del 4-aminobenzoato, y también de un ácido de referencia, la warfarina y una serie de ácidos homólogos derivados de paraben. Los congéneres seleccionados para ambas series son de peso molecular creciente con lo que el estudio comprende un amplio intervalo de solubilidad. Los resultados obtenidos para los dos compuestos de referencia son concordantes con los que ofrece la literatura. Se ha determinado la solubilidad cinética y la solubilidad intrínseca para todas las sustancias seleccionadas y se ha realizado un estudio amplio sobre la cantidad óptima de compuesto para realizar las medidas experimentales. Este estudio incluye la valoración de los resultados obtenidos al trabajar con cantidades crecientes de muestra y la evaluación de las cantidades límite para el trabajo experimental.

En consecuencia, se confirma que la solubilidad termodinámica para la especie neutra, solubilidad intrínseca, muestra un valor constante cuando la función de Bjerrum se mantiene entre 0,2 y 0,8 para el " CheqPoint" (el punto experimental para la medición efectiva) y el error experimental que afecta a los resultados aumenta significativamente si se trabaja fuera de estos límites. Hay que puntualizar aquí que los ácidos en estudio muestran valores de pK_a cercanos a 8 con lo que el desplazamiento de las curvas de valoración debido a la precipitación permite en todos los casos trabajar en un intervalo de *pH* adecuado. Sin embargo la serie de bases seleccionada muestra valores de pK_a de la base protonada del orden de 2.5 con lo que si la cantidad de muestra es relativamente grande resulta necesario llegar a valores de *pH* muy ácidos para conseguir la disolución completa de la muestra. Además, para compuestos relativamente insolubles, el desplazamiento de las curvas de valoración alcanza con facilidad la región de *pH* muy ácida y no es posible realizar medidas con la exactitud requerida.

3) Determinación del perfil de solubilidad con el *pH* de algunos fármacos en solución acuosa

Con el objetivo de evaluar la metodología potenciométrica para la determinación del perfil de solubilidad con el *pH* de fármacos diversos, se han seleccionado cinco fármacos ionizables de naturaleza diferente, un ácido y una base monopróticos (propilparaben y acebutolol), una base diprótica (quetiapina) y dos compuestos anfóteros que muestran una especie iónica zwitteriónica cada uno (sulfadimetoxina y cefadroxil). Los perfiles de solubilidad en función del *pH* se han determinado mediante dos metodologías diferentes: la clásica de equilibración (Shake-Flask, S-F) y el método potenciométrico conocido como CheqSol. En ambos casos se han utilizado las ecuaciones de Henderson-Hasselbalch (H-H) apropiadas u otras directamente relacionadas con ellas. Los resultados obtenidos de forma independiente por ambos métodos son concordantes para la mayoría de las condiciones experimentales ensayadas. Sin embargo, en algunos casos se han observado discrepancias que han llevado a una revisión crítica acerca de la

influencia del electrolito utilizado como agente amortiguador en el método S-F. Así, algunas desviaciones de los puntos experimentales con respecto a los perfiles H-H pueden atribuirse a las interacciones específicas entre el fármaco y el tampón utilizado debido al carácter hidrotrófico de éste último, como es el caso de los ácidos cítrico y láctico a *pH* inferior a 3 con los fármacos propilparaben, sulfadimetoxina y cefadroxil. Las desviaciones observadas desaconsejan el uso de los tampones mencionados para determinar la solubilidad en medio ácido. En otros casos, las desviaciones observadas son independientes de los tampones utilizados ya que son provocadas por la formación de nuevas especies tales como agregados iónicos (cefadroxil) o a la precipitación de una sal de alguna especie catiónica del compuesto analizado (quetiapina). Los resultados obtenidos en este trabajo demuestran la idoneidad del método potenciométrico para lograr valores confiables de solubilidad intrínseca y perfiles de solubilidad con el *pH*. Sin embargo, cuando existen reacciones secundarias, tales como la formación de agregados iónicos (caso del cefadroxil a valores de *pH* superiores a 6,5), o en el intervalo de *pH* en estudio se forma más de un precipitado (caso de la quetiapina), el programa CheqSol, asociado a la técnica potenciométrica, no es capaz de detectarlas y el perfil de solubilidad obtenido no está de acuerdo con la variación de solubilidad real con el *pH* de la solución.

En consecuencia, se concluye que la técnica potenciométrica y el programa CheqSol asociado permiten una buena determinación del perfil de solubilidad con el *pH* siempre que no haya reacciones secundarias asociadas. Es decir, para la aplicación correcta de la metodología potenciométrica hay que conocer bien la química del compuesto estudiado.

4) Estudio sobre la velocidad de disolución de la Amphotericina B

Con el objetivo de aumentar la biodisponibilidad de un fármaco muy insoluble tomado como modelo, la Amphotericina B, se ha realizado un estudio sobre el aumento de su velocidad de disolución en función de su forma de preparación. En

concreto, se han preparado dispersiones sólidas con y sin portador del fármaco y también con y sin la presencia de tensioactivo. Se han ensayado dos tipos de portador, manitol e inulina, y dos tipos de tensioactivo, lauril sulfato de sodio (SLS) y deoxicolato de sodio (SDC). La difracción de rayos X reveló que la Amphotericina B se encontraba en estado amorfo en todas las dispersiones sólidas estudiadas. Se ha medido la velocidad de disolución de los comprimidos preparados a partir de los diversos tipos de dispersiones sólidas en dos medios diferentes, en agua y en medio ácido, y se observó que la velocidad de disolución del fármaco en soluciones acuosas ácidas se incrementa significativamente en presencia de fármaco-portador y de tensioactivo. La diferencia en la velocidad de disolución debida al tensioactivo es evidente solamente en el caso de soluciones acuosas y no en medio ácido.

En resumen, la mayor velocidad de disolución en solución acuosa se alcanza para los comprimidos preparados a partir de dispersiones sólidas con manitol como vehículo y SDC como agente tensioactivo. Sin embargo, la disolución del fármaco en estas condiciones no es suficiente para ser considerada satisfactoria y se requiere todavía un trabajo de profundización en el estudio descrito en esta tesis para conseguir una forma de preparación farmacéutica que permita una liberación de más completa del fármaco.

Apéndice

Tabla 1-1A. Valores interpolados de ${}^{s}_{s}pK_a$ del ácido benzoico en diversas mezclas metanol/agua (0–50% w/w) a varias temperaturas (25-55°C)

T (°C)	MeOH% (w/w)	pK_a (I)	I	ε_{mezcla}	$\varepsilon_{(H2O)}$	d_{mezcla}	$d_{(H2O)}$	A	a_oB	log γ	pK_a (I=0)
25.2	10	4.14	0.198	74.16	78.38	0.9804	0.9963	0.55	1.53	-0.147	4.44
25.2	20	4.32	0.198	69.84	78.38	0.9648	0.9963	0.61	1.56	-0.159	4.64
25.2	30	4.53	0.198	65.42	78.38	0.9487	0.9963	0.67	1.60	-0.174	4.88
25.2	40	4.77	0.198	60.90	78.38	0.9315	0.9963	0.74	1.65	-0.191	5.15
25.2	50	5.05	0.198	56.27	78.38	0.9125	0.9963	0.84	1.69	-0.213	5.47
29.6	10	4.17	0.168	72.62	76.81	0.9790	0.9952	0.56	1.53	-0.141	4.45
29.6	20	4.34	0.168	68.33	76.81	0.9630	0.9952	0.61	1.56	-0.153	4.65
29.6	30	4.54	0.168	63.96	76.81	0.9465	0.9952	0.68	1.60	-0.168	4.88
29.6	40	4.77	0.168	59.49	76.81	0.9289	0.9952	0.75	1.65	-0.185	5.14
29.6	50	5.04	0.168	54.93	76.81	0.9095	0.9952	0.85	1.70	-0.206	5.45
34.4	10	4.18	0.177	70.92	75.08	0.9773	0.9939	0.57	1.53	-0.145	4.47
34.4	20	4.36	0.177	66.68	75.08	0.9608	0.9939	0.62	1.56	-0.158	4.67
34.4	30	4.56	0.177	62.35	75.08	0.9439	0.9939	0.69	1.60	-0.173	4.90
34.4	40	4.79	0.177	57.95	75.08	0.9258	0.9939	0.77	1.65	-0.191	5.17
34.4	50	5.07	0.177	53.46	75.08	0.9060	0.9939	0.87	1.70	-0.212	5.49
39.9	10	4.19	0.172	69.07	73.19	0.9752	0.9923	0.57	1.53	-0.146	4.48
39.9	20	4.35	0.172	64.87	73.19	0.9582	0.9923	0.63	1.57	-0.159	4.66
39.9	30	4.53	0.172	60.60	73.19	0.9407	0.9923	0.70	1.61	-0.174	4.88
39.9	40	4.74	0.172	56.27	73.19	0.9222	0.9923	0.78	1.65	-0.192	5.12
39.9	50	4.99	0.172	51.86	73.19	0.9019	0.9923	0.88	1.70	-0.215	5.42
44.5	10	4.22	0.183	67.54	71.63	0.9732	0.9907	0.58	1.53	-0.150	4.52
44.5	20	4.38	0.183	63.39	71.63	0.9558	0.9907	0.64	1.57	-0.164	4.71
44.5	30	4.56	0.183	59.17	71.63	0.9379	0.9907	0.71	1.61	-0.180	4.92
44.5	40	4.77	0.183	54.89	71.63	0.9190	0.9907	0.79	1.65	-0.199	5.17
44.5	50	5.02	0.183	50.54	71.63	0.8983	0.9907	0.90	1.70	-0.222	5.46
49.4	10	4.30	0.166	65.96	70.02	0.9710	0.9889	0.59	1.53	-0.148	4.59
49.4	20	4.46	0.166	61.85	70.02	0.9531	0.9889	0.65	1.57	-0.161	4.78
49.4	30	4.64	0.166	57.68	70.02	0.9348	0.9889	0.72	1.61	-0.177	4.99
49.4	40	4.85	0.166	53.46	70.02	0.9155	0.9889	0.81	1.65	-0.196	5.24
49.4	50	5.10	0.166	49.19	70.02	0.8945	0.9889	0.91	1.70	-0.220	5.53
54.5	10	4.33	0.165	64.34	68.36	0.9684	0.9868	0.60	1.53	-0.149	4.63
54.5	20	4.47	0.165	60.27	68.36	0.9502	0.9868	0.66	1.57	-0.163	4.80
54.5	30	4.63	0.165	56.16	68.36	0.9314	0.9868	0.73	1.61	-0.180	4.98
54.5	40	4.81	0.165	52.00	68.36	0.9117	0.9868	0.82	1.65	-0.199	5.20
54.5	50	5.02	0.165	47.80	68.36	0.8904	0.9868	0.93	1.70	-0.224	5.46

Tabla 1-2A. Valores interpolados de $^{s}_{s}pK_a$ del ácido acético en diversas mezclas metanol/agua (0–50% w/w) a varias temperaturas (25-55°C)

T (°C)	MeOH% (w/w)	pK_a (I)	I	ε_{mezcla}	$\varepsilon_{(H2O)}$	d_{mezcla}	$d_{(H2O)}$	A	a_oB	log γ	pK_a (I=0)
25.2	0	4.56	0.168	78.39	78.39	0.9963	0.9963	0.51	1.50	-0.129	4.81
25.2	10	4.69	0.168	74.17	78.39	0.9805	0.9963	0.55	1.53	-0.140	4.97
25.2	20	4.84	0.168	69.85	78.39	0.9648	0.9963	0.61	1.56	-0.151	5.14
25.2	30	5.01	0.168	65.43	78.39	0.9488	0.9963	0.67	1.60	-0.166	5.34
25.2	40	5.20	0.168	60.90	78.39	0.9316	0.9963	0.74	1.65	-0.182	5.57
25.2	50	5.43	0.168	56.28	78.39	0.9125	0.9963	0.84	1.69	-0.203	5.84
30.5	0	4.58	0.168	76.48	76.48	0.9950	0.9950	0.52	1.50	-0.131	4.84
30.5	10	4.71	0.168	72.30	76.48	0.9787	0.9950	0.56	1.53	-0.141	4.99
30.5	20	4.85	0.168	68.02	76.48	0.9626	0.9950	0.61	1.56	-0.153	5.16
30.5	30	5.01	0.168	63.65	76.48	0.9460	0.9950	0.68	1.60	-0.168	5.35
30.5	40	5.20	0.168	59.20	76.48	0.9283	0.9950	0.76	1.65	-0.185	5.57
30.5	50	5.42	0.168	54.65	76.48	0.9089	0.9950	0.85	1.70	-0.206	5.83
34.7	0	4.57	0.173	74.99	74.99	0.9938	0.9938	0.52	1.50	-0.133	4.84
34.7	10	4.69	0.173	70.83	74.99	0.9772	0.9938	0.57	1.53	-0.144	4.98
34.7	20	4.82	0.173	66.59	74.99	0.9607	0.9938	0.62	1.57	-0.157	5.13
34.7	30	4.97	0.173	62.27	74.99	0.9437	0.9938	0.69	1.60	-0.171	5.31
34.7	40	5.14	0.173	57.86	74.99	0.9256	0.9938	0.77	1.65	-0.189	5.52
34.7	50	5.34	0.173	53.38	74.99	0.9058	0.9938	0.87	1.70	-0.211	5.76
39.8	0	4.63	0.176	73.22	73.22	0.9923	0.9923	0.53	1.50	-0.135	4.90
39.8	10	4.74	0.176	69.10	73.22	0.9752	0.9923	0.57	1.53	-0.147	5.04
39.8	20	4.87	0.176	64.90	73.22	0.9582	0.9923	0.63	1.57	-0.160	5.19
39.8	30	5.02	0.176	60.63	73.22	0.9408	0.9923	0.70	1.61	-0.175	5.37
39.8	40	5.19	0.176	56.30	73.22	0.9222	0.9923	0.78	1.65	-0.193	5.58
39.8	50	5.39	0.176	51.89	73.22	0.9020	0.9923	0.88	1.70	-0.216	5.83
44.5	0	4.74	0.168	71.63	71.63	0.9907	0.9907	0.53	1.50	-0.135	5.01
44.5	10	4.85	0.168	67.54	71.63	0.9732	0.9907	0.58	1.53	-0.146	5.14
44.5	20	4.98	0.168	63.39	71.63	0.9558	0.9907	0.64	1.57	-0.159	5.29
44.5	30	5.12	0.168	59.17	71.63	0.9379	0.9907	0.71	1.61	-0.175	5.47
44.5	40	5.28	0.168	54.89	71.63	0.9190	0.9907	0.79	1.65	-0.194	5.67
44.5	50	5.47	0.168	50.54	71.63	0.8983	0.9907	0.90	1.70	-0.217	5.90
49.5	0	4.77	0.170	69.98	69.98	0.9888	0.9888	0.54	1.50	-0.137	5.04
49.5	10	4.87	0.170	65.92	69.98	0.9709	0.9888	0.59	1.53	-0.149	5.17
49.5	20	5.00	0.170	61.81	69.98	0.9530	0.9888	0.65	1.57	-0.162	5.32
49.5	30	5.13	0.170	57.64	69.98	0.9347	0.9888	0.72	1.61	-0.179	5.49
49.5	40	5.29	0.170	53.42	69.98	0.9154	0.9888	0.81	1.65	-0.198	5.69
49.5	50	5.47	0.170	49.15	69.98	0.8944	0.9888	0.91	1.70	-0.221	5.92
54.5	0	4.71	0.168	68.36	68.36	0.9868	0.9868	0.54	1.50	-0.138	4.99
54.5	10	4.83	0.168	64.34	68.36	0.9684	0.9868	0.60	1.53	-0.150	5.13
54.5	20	4.97	0.168	60.27	68.36	0.9502	0.9868	0.66	1.57	-0.164	5.30
54.5	30	5.12	0.168	56.16	68.36	0.9314	0.9868	0.73	1.61	-0.181	5.48
54.5	40	5.30	0.168	52.00	68.36	0.9117	0.9868	0.82	1.65	-0.200	5.70
54.5	50	5.50	0.168	47.80	68.36	0.8904	0.9868	0.93	1.70	-0.225	5.95

Tabla 2-1A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) de la warfarina (Fw=308.33 g/mol; pK_a=4.88)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.0101	5.48	0.48	109
0.0104	6.59	0.70	139
0.0118	5.92	0.45	119
0.0100	5.40	0.42	106
0.0105	4.89	0.51	107
0.0103	5.76	0.48	123
0.0173	6.58	0.35	98
0.0103	7.10	0.49	108
0.0200	5.86	0.26	99
0.0057	5.90	0.64	88
0.0311	6.50	0.21	18
0.0249	6.306	0.32	131

Tabla 2-2A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) de la lidocaína (Fw=234.3 g/mol; pK_a=7.98)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.1061	3058	0.5	3196
0.1053	3072	0.47	4709
0.144	3036	0.6	3177
0.146	3090	0.58	3226
0.1857	3144	0.64	5251
0.1837	3006	0.66	5014
0.2123	3045	0.65	5122
0.2005	3239	0.67	3315
0.2573	3316	0.74	3343
0.2633	2995	0.76	3053
0.2624	3069	0.75	4534
0.124	2962	0.55	3308
0.0755	3031	0.32	4267
0.088	2997	0.4	3683
0.1086	3056	0.46	3325
0.17	3250	0.61	3648

Tabla 2-3A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del metilparaben (Fw=152.18 g/mol; pK_a=8.15)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.3944	2639	0.35	5918
0.2488	2231	0.39	2598
0.4065	2253	0.4	4999
0.3569	2004	0.41	3596
0.351	2270	0.49	6347
0.3518	2065	0.49	5728
0.2529	2094	0.5	3158
0.2045	2144	0.54	3232
0.2985	2166	0.65	2555
0.4012	2555	0.65	3483
0.2023	2513	0.65	3101
0.2541	1933	0.66	3159
0.1515	1905	0.67	4643
0.1937	2097	0.67	3502
0.2936	2025	0.73	3241
0.1008	2310	0.75	4301
0.1461	2238	0.75	4135

Tabla 2-4A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del etilparaben (Fw=166.18 g/mol; pK_a=8.18)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.2061	929.8	0.2	2197
0.1488	950.7	0.25	1883
0.2567	805.7	0.25	883
0.1259	958	0.26	1700
0.1276	920.6	0.26	1439
0.1249	972.1	0.27	2360
0.2279	818	0.27	1434
0.1475	814.1	0.31	1226
0.0923	928	0.33	1357
0.1771	883.9	0.33	2322
0.0915	818	0.34	1222
0.1479	908.1	0.34	2014
0.1523	964.2	0.34	1954
0.0965	828.6	0.36	1531
0.155	968	0.36	1500
0.1072	881.4	0.375	1667
0.1261	827	0.375	1705
0.0953	913.7	0.41	1410
0.0671	921.4	0.43	1417
0.0898	924.7	0.43	2127
0.0745	820.4	0.44	1680
0.0743	886.8	0.5	2081
0.0884	922.3	0.5	1596
0.0557	872.9	0.56	1363
0.0487	918.9	0.61	1635
0.0481	918.3	0.69	1813
0.0426	858.4	0.71	2351

Tabla 2-5A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del propilparaben (Fw=180.21 g/mol; pK_a=8.16)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.0786	328	0.2	361
0.1222	345	0.2	591
0.0828	267	0.22	289
0.1037	362	0.22	1179
0.0726	333	0.24	358
0.0622	292	0.3	1065
0.0633	340	0.3	1185
0.0711	331	0.3	822
0.0664	291	0.32	993
0.0502	291	0.35	1059
0.0578	356	0.35	445
0.06	281	0.35	865
0.0471	346	0.4	1212
0.0518	279	0.4	1034
0.0556	325	0.4	1137
0.0525	340	0.43	1117
0.0408	317	0.45	591
0.0442	287	0.45	686
0.044	324	0.48	1021
0.0304	412	0.5	935
0.0352	344	0.55	872
0.0397	342	0.56	1220
0.0249	328	0.78	706

Tabla 2-6A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del butilparaben (Fw=194.2 g/mol; pK_a=8.18)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.0965	230.2	0.2	459
0.0589	237.6	0.25	471
0.0952	228.5	0.25	430
0.0993	229.6	0.25	425
0.0674	221.5	0.26	464
0.0654	221.8	0.3	428
0.0456	212.3	0.32	413
0.0397	208.0	0.35	415
0.0541	216.7	0.35	445
0.0316	206	0.4	453
0.0394	216.1	0.4	418
0.0306	220.9	0.45	459
0.0326	221.9	0.45	443
0.0376	213.6	0.45	447
0.0445	221.1	0.47	464
0.0129	240.4	0.5	472
0.0228	218.1	0.5	442
0.0244	219.1	0.55	439
0.0126	189.6	0.56	396
0.0229	213.5	0.6	470
0.0254	214.7	0.65	474
0.0105	240.7	0.69	479
0.017	235.8	0.72	488
0.0183	220.5	0.75	479
0.0107	229.4	0.8	478

Tabla 2-7A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del methyl 4-aminobenzoate (Fw=151.16 g/mol; pK_a=2.66)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.10027	1142	0.45	1986
0.05226	1133	0.22	1666
0.04061	1299	0.25	3047
0.07067	1190	0.54	1785
0.0858	1247	0.43	1983
0.20756	1124	0.80	1410
0.07060	1169	0.60	1818
0.16233	1142	0.73	1498
0.18077	1084	0.77	1512
0.25204	1226	0.79	1399
0.30334	1176	0.83	1533
0.0406	1613	0.1	4824
0.0505	1160	0.27	1924
0.0967	1137	0.67	1593
0.0750	1161	0.50	1639
0.1461	1235	0.85	1637
0.1292	1238	0.85	1577
0.1387	1345	0.85	1642
0.1195	1108	0.87	1534
0.1268	1285	0.77	1614
0.1475	1150	0.83	1396
0.0434	1508	0.20	2450
0.0466	1257	0.25	2133
0.1092	1152	0.80	1488

Tabla 2-8A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) de la benzocaine (Fw=165.19 g/mol; pK_a=2.67)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.0888	846.8	0.85	1047
0.0836	846.2	0.83	1056
0.0721	818.0	0.78	994
0.0574	803.7	0.73	986
0.0517	832.1	0.78	1116
0.0208	818.6	0.32	1655
0.0410	776.7	0.63	1009
0.0197	935.3	0.13	1804
0.0311	800.8	0.50	1001
0.0467	850.0	0.71	1148
0.0549	848.8	0.65	1021
0.0307	706.5	0.55	1626
0.0403	699.5	0.68	1102
0.0504	724.6	0.77	1145
0.0412	714.4	0.70	714
0.0707	722.0	0.80	1034
0.0815	736.2	0.81	818
0.1008	726.7	0.85	1132
0.0613	755.2	0.77	956
0.0199	740.8	0.36	3144
0.0260	765.2	0.53	1291
0.0298	832.8	0.53	1125
0.0352	784.4	0.57	1730

Tabla 2-9A. Solubilidad intrínseca (S_o) y solubilidad cinética (S_K) del butamben (Fw=193.242 g/mol; pK_a=2.56)

Muestra (wt./g)	S_o (µg/mL)	$\bar{n}$	S_K (µg/mL)
0.0053	171.4	0.4	315
0.0100	170.4	0.5	301
0.1080	203	0.7	393
0.0041	139.6	0.35	---
0.0070	159.7	0.45	287
0.0062	153.2	0.50	299
0.0073	171.3	0.50	177

Tabla 3-1A. Perfil solubilidad-*pH* del propilparaben obtenido mediante el método de equilibración (S-F)

Tampón	*pH* inicial	*pH* equilibrio	S[a] (µg/ml)	s[a]	%RSD	S (mol/L)	log S
H_3Cit/H_2Cit^-	2.22	2.53	395.6	1.2	0.30	2.20E-03	-2.659
H_3Cit/H_2Cit^-	2.49	2.55	385.7	2.5	0.65	2.14E-03	-2.670
$HLac/Lac^-$	2.48	2.55	347.4	1.3	0.30	1.93E-03	-2.715
$H_3PO_4/H_2PO_4^-$	2.61	2.56	273.9	10.9	3.99	1.52E-03	-2.818
$HFor/For^-$	2.77	2.67	290.7	9.8	3.39	1.61E-03	-2.792
$HLac/Lac^-$	2.61	2.70	347.0	4.0	0.30	1.93E-03	-2.715
H3Cit/H2Cit-	2.75	2.76	370.1	1.5	0.41	2.05E-03	-2.687
$HLac/Lac^-$	3.08	3.01	337.3	0.4	0.30	1.87E-03	-2.728
H_3Cit/H_2Cit^-	3.20	3.21	342.4	3.1	0.92	1.90E-03	-2.721
$HLac/Lac^-$	3.48	3.43	336.6	1.0	0.30	1.87E-03	-2.729
HAc/Ac^-	3.75	3.58	297.5	13.0	4.36	1.65E-03	-2.782
$H_2Cit^-/HCit_2^-$	3.81	4.01	323.1	0.6	0.19	1.79E-03	-2.746
$H_2Cit^-/HCit_2^-$	4.01	4.03	325.4	5.0	1.53	1.81E-03	-2.743
$H_2Cit^-/HCit_2^-$	4.53	4.55	317.3	3.7	1.18	1.76E-03	-2.754
HAc/Ac^-	4.87	4.73	296.0	11.3	3.80	1.64E-03	-2.784
$HCit_2^-/Cit_3^-$	4.76	4.92	324.5	0.7	0.22	1.80E-03	-2.745
$H_2Cit^-/HCit_2^-$	4.95	5.00	330.4	10.1	3.07	1.83E-03	-2.737
$H_2Cit^-/HCit_2^-$	5.33	5.48	302.3	0.5	0.17	1.68E-03	-2.775
$H_2Cit^-/HCit_2^-$	5.50	5.52	300.7	5.9	1.95	1.67E-03	-2.778
HCit2-/Cit3-	6.03	6.04	306.0	5.1	1.67	1.70E-03	-2.770
$H_2PO_4^-/HPO_4^{2}$	6.87	6.65	307.1	4.0	1.31	1.70E-03	-2.768
$HCit_2^-/Cit_3^-$	6.70	6.69	304.3	0.3	0.10	1.69E-03	-2.772
$HCit_2^-/Cit_3^-$	7.00	6.99	310.2	2.1	0.68	1.72E-03	-2.764
$H_2PO_4^-/HPO_4^{2-}$	7.86	7.57	357.1	17.9	5.03	1.98E-03	-2.703
H_2BO_3/HBO_2^-	9.03	8.70	1273.7	28.6	2.24	7.07E-03	-2.151
NH_4^+/ NH_3	9.31	8.81	1875.1	32.9	1.75	1.04E-02	-1.983
H_2BO_3/HBO_2^-	9.92	9.27	3580.0	258.5	7.22	1.99E-02	-1.702
NH_4^+/ NH_3	10.29	9.36	5246.8	103.2	1.97	2.91E-02	-1.536

[a]S y s simbolizan, respectivamente, el valor medio y la desviación estandard de tres medidas independientes realizadas después de 24, 42 y 78 horas de equilibración

Tabla 3-2A. Perfil solubilidad-*pH* del acebutolol obtenido mediante el método de equilibración (S-F)

Tampón	*pH* inicial	*pH* equilibrio	S[a] (µg/ml)	s[a]	%RSD	S (mol/L)	log S
NH_4^+/ NH_3	9.54	9.15	2784.2	225.8	8.11	8.28E-03	-2.082
H_2BO_3/HBO_2^-	9.68	9.29	1819.4	42.0	2.31	5.41E-03	-2.267
H_2BO_3/HBO_2^-	9.91	9.35	1450.5	28.6	1.97	4.31E-03	-2.365
NH_4^+/ NH_3	9.81	9.37	1530.5	55.6	3.63	4.55E-03	-2.342
H_2BO_3/HBO_2^-	9.85	9.60	1216.6	25.1	2.06	3.62E-03	-2.442
NH_4^+/ NH_3	9.93	9.63	1130.9	44.2	3.91	3.36E-03	-2.473
HPO_4^{2-}/PO_4^{3-}	10.06	9.68	1017.9	14.2	1.39	3.03E-03	-2.519
H_2BO_3/HBO_2^-	10.05	9.72	979.2	15.7	1.61	2.91E-03	-2.536
H_2BO_3/HBO_2^-	10.11	9.76	824.3	21.5	2.61	2.45E-03	-2.611
NH_4^+/ NH_3	10.19	9.86	812.1	88.0	10.84	2.41E-03	-2.617
NH_4^+/ NH_3	10.43	9.97	756.6	21.3	2.81	2.25E-03	-2.648
NH_4^+/ NH_3	10.74	10.26	681.8	47.0	6.89	2.03E-03	-2.693
HPO_4^{2-}/PO_4^{3-}	11.37	10.94	570.5	50.9	8.92	1.70E-03	-2.771
HPO_4^{2-}/PO_4^{3-}	11.69	11.46	564.7	21.9	3.88	1.68E-03	-2.775
HPO_4^{2-}/PO_4^{3-}	12.01	11.86	566.0	18.8	3.33	1.68E-03	-2.774

[a]S y s simbolizan, respectivamente, el valor medio y la desviación estandard de tres medidas independientes realizadas después de 24, 42 y 78 horas de equilibración

Tabla 3-3A. Perfil solubilidad-*pH* de la quetiapina obtenido mediante el método de equilibración (S-F)

Tampón	*pH* inicial	*pH* equilibrio	S (μg/ml)	s[a]	%RSD	S (mol/L)	log S
HLac/Lac^-	2,60	3,67	10868,9	53,6	0,49	2,83E-02	-1,548
HLac/Lac^-	2,76	3,69	10406,3	598,7	5,75	2,71E-02	-1,566
HLac/Lac^-	3,08	3,82	9239,8	857,4	9,28	2,41E-02	-1,618
HLac/Lac^-	3,48	3,88	7723,7	96,5	1,25	2,01E-02	-1,696
HFor/For^-	3,66	4,02	7219,5	381,1	5,28	1,88E-02	-1,725
HAc/Ac^-	3,73	4,03	7634,3	2,3	0,03	1,99E-02	-1,701
HAc/Ac^-	4,87	4,87	4380,0	14,8	0,34	1,14E-02	-1,942
$H_2PO_4^-/HPO_4^{2-}$	6,35	5,77	3494,9	3,2	0,09	9,11E-03	-2,040
$H_2PO_4^-/HPO_4^{2-}$	6,50	6,31	2822,6	70,1	2,48	7,36E-03	-2,133
$H_2PO_4^-/HPO_4^{2-}$	7,63	7,04	1058,2	63,4	5,99	2,76E-03	-2,559
$H_2PO_4^-/HPO_4^{2-}$	10,75	7,16	881,4	79,7	9,04	2,30E-03	-2,639
H_2BO_3/HBO_2^-	8,82	8,76	477,4	19,8	4,15	1,24E-03	-2,905
NH_4^+/ NH_3	9,14	9,06	421,4	18,4	4,36	1,10E-03	-2,959
H_2BO_3/HBO_2^-	9,83	9,79	509,4	66,8	13,11	1,33E-03	-2,877
NH_4^+/ NH_3	10,16	9,98	500,3	2,1	0,42	1,30E-03	-2,885
HPO_4^{2-}/PO_4^{3-}	11,81	11,30	574,9	58,6	10,19	1,50E-03	-2,824

[a]S y s simbolizan, respectivamente, el valor medio y la desviación estandard de tres medidas independientes realizadas después de 24, 42 y 78 horas de equilibración

Tabla 3-4A. Perfil solubilidad-*pH* de la sulfadimetoxine obtenido mediante el método de equilibración (S-F)

Tampón	*pH* inicial	*pH* equilibrio	S[a] (μg/ml)	s[a]	%RSD	S (mol/L)	log S
$H_3PO4/H_2PO_4^-$	1,62	1,89	37,2	0,3	0,85	1,20E-04	-3,921
$H_3PO4/H_2PO_4^-$	1,73	2,08	31,9	0,2	0,74	1,03E-04	-3,988
$H_3PO4/H_2PO_4^-$	2,09	2,37	25,2	0,4	1,75	8,12E-05	-4,090
$HFor/For^-$	2,21	2,50	23,6	0,1	0,31	7,60E-05	-4,119
$HLac/Lac^-$	2,48	2,54	24,7	0,5	1,94	7,95E-05	-4,100
H_3Cit/H_2Cit^-	2,62	2,54	33,0	0,1	0,32	1,06E-04	-3,974
$HLac/Lac^-$	2,61	2,70	21,8	0,6	2,56	7,03E-05	-4,153
H_3Cit/H_2Cit^-	2,83	2,73	26,2	0,1	0,51	8,44E-05	-4,073
$H_3PO_4/H_2PO_4^-$	2,63	2,87	19,4	0,0	0,13	6,26E-05	-4,203
$HLac/Lac^-$	2,97	3,03	19,2	0,1	0,53	6,20E-05	-4,207
H_3Cit/H_2Cit^-	3,19	3,16	19,9	0,3	1,55	6,42E-05	-4,192
$HFor/For^-$	3,11	3,27	19,4	0,1	0,55	6,26E-05	-4,203
$HLac/Lac^-$	3,39	3,49	18,1	0,3	1,58	5,83E-05	-4,235
$HFor/For^-$	3,66	3,75	18,7	0,1	0,56	6,04E-05	-4,219
$H_2Cit^-/HCit^{2-}$	4,07	4,00	18,0	0,2	1,30	5,80E-05	-4,237
$HFor/For^-$	4,20	4,30	18,7	0,1	0,45	6,01E-05	-4,221
$H_2Cit^-/HCit^{2-}$	4,59	4,51	18,1	0,4	1,97	5,85E-05	-4,233
Hac/Ac^-	4,64	4,75	20,1	0,3	1,36	6,48E-05	-4,189
$H_2Cit^-/HCit^{2-}$	5,26	5,21	19,6	0,1	0,42	6,31E-05	-4,200
Hac/Ac^-	5,24	5,23	21,7	0,2	1,13	7,00E-05	-4,155
Hac/Ac^-	5,22	5,23	22,0	0,4	1,81	7,10E-05	-4,149
$HCit^{2-}/Cit^{3-}$	5,75	5,79	26,4	0,1	0,37	8,51E-05	-4,070
$H_2PO_4^-/HPO_4^{2-}$	5,99	5,96	34,3	0,5	1,38	1,11E-04	-3,956
$HCit^{2-}/Cit^{3-}$	6,05	6,02	33,4	0,2	0,51	1,08E-04	-3,968
$H_2PO_4^-/HPO_4^{2-}$	6,41	6,37	57,1	1,6	2,72	1,84E-04	-3,735
$H_2PO_4^-/HPO_4^{2-}$	6,60	6,55	78,3	2,7	3,49	2,52E-04	-3,598
$HCit^{2-}/Cit^{3-}$	6,70	6,64	90,7	0,3	0,28	2,92E-04	-3,534
$H_2PO_4^-/HPO_4^{2-}$	6,86	6,74	112,0	3,9	3,46	3,61E-04	-3,443
$HCit^{2-}/Cit^{3-}$	7,03	6,87	162,7	0,9	0,53	5,24E-04	-3,280
$H_2PO_4^-/HPO_4^{2-}$	7,01	6,93	157,2	4,9	3,09	5,06E-04	-3,295
$H_2PO_4^-/HPO_4^{2-}$	7,61	7,28	324,8	11,7	3,59	1,05E-03	-2,980
$H_2PO_4^-/HPO_4^{2-}$	7,93	7,37	409,4	11,7	2,85	1,32E-03	-2,880
NH_4^+/ NH_3	8,52	7,99	1714,3	175,4	10,23	5,52E-03	-2,258
H_2BO_3/HBO_2^-	8,48	8,15	2579,0	135,0	5,23	8,31E-03	-2,080
H_2BO_3/HBO_2^-	9,19	8,56	6914,4	274,3	3,97	2,23E-02	-1,652
NH_4^+/ NH_3	9,57	8,74	10750,2	102,2	0,95	3,46E-02	-1,460

[a]S y s simbolizan, respectivamente, el valor medio y la desviación estandard de tres medidas independientes realizadas después de 24, 42 y 78 horas de equilibración

Tabla 3-5A. Perfil solubilidad-*pH* del cefadroxil obtenido mediante el método de equilibración (S-F)

Tampón	*pH* inicial	*pH* equilibrio	S[a] (µg/ml)	s[a]	%RSD	S (mol/L)	log S
H_3Cit/H_2Cit^-	2,55	2,81	33,2	54,3	0,16	9,12E-02	-1,040
$H_2Cit^-/HCit^{2-}$	2,79	2,98	25,9	644,4	2,48	7,14E-02	-1,146
$HFor/For^-$	2,77	3,00	18,1	461,6	2,56	4,97E-02	-1,304
$HLac/Lac^-$	2,48	3,07	21,1	144,2	0,16	5,81E-02	-1,236
H_3PO_4/H_2PO^{4-}	2,61	3,11	16,4	547,7	3,34	4,51E-02	-1,346
$HLac/Lac^-$	2,61	3,19	23,2	131,0	0,16	6,38E-02	-1,195
$HLac/Lac^-$	2,97	3,36	21,4	246,8	0,16	5,90E-02	-1,229
$HFor/For^-$	3,39	3,38	15,0	169,7	1,13	4,14E-02	-1,383
H_3Cit/H_2Cit^-	3,25	3,47	16,4	277,9	1,70	4,51E-02	-1,346
$HLac/Lac^-$	3,39	3,63	19,3	312,8	0,16	5,32E-02	-1,274
Hac/Ac^-	3,73	3,67	14,7	477,2	3,26	4,03E-02	-1,394
$H_2Cit^-/HCit^{2-}$	4,03	4,13	14,3	209,9	1,47	3,93E-02	-1,406
$H_2Cit^-/HCit^{2-}$	4,55	4,59	14,7	20,3	0,14	4,03E-02	-1,394
Hac/Ac^-	4,87	4,70	13,2	399,9	3,04	3,62E-02	-1,441
$H_2Cit^-/HCit^{2-}$	4,98	4,81	13,0	194,7	1,50	3,58E-02	-1,446
$H_2PO_4^-/HPO_4^{2-}$	6,35	4,96	12,4	559,7	4,50	3,42E-02	-1,466
HCit2-/Cit3-	5,50	5,43	15,0	404,3	2,69	4,14E-02	-1,383
$H_2PO_4^-/HPO_4^{2-}$	6,87	5,57	13,5	306,8	2,27	3,71E-02	-1,430
$H_2PO_4^-/HPO_4^{2-}$	7,86	5,84	14,4	357,4	2,48	3,97E-02	-1,401
$HCit^{2-}/Cit^{3-}$	6,03	5,95	15,0	192,1	1,28	4,14E-02	-1,384
$HCit^{2-}/Cit^{3-}$	6,69	6,31	16,0	254,4	1,59	4,39E-02	-1,357
$HCit^{2-}/Cit^{3-}$	7,03	6,38	16,7	354,5	2,12	4,59E-02	-1,338
$H_2PO_4^-/HPO_4^{2-}$	8,94	6,50	22,5	140,7	3,34	6,20E-02	-1,208
$H_2PO_4^-/HPO_4^{2-}$	8,24	6,52	22,3	187,1	3,34	6,12E-02	-1,213
$H_2PO_4^-/HPO_4^{2-}$	8,62	6,59	22,4	73,8	3,34	6,17E-02	-1,209
NH_4^+/ NH_3	9,31	6,63	29,6	366,0	1,23	8,16E-02	-1,088
H_2BO_3/HBO_2^-	9,07	6,74	35,3	740,7	2,10	9,71E-02	-1,013

[a]S y s simbolizan, respectivamente, el valor medio y la desviación estandard de tres medidas independientes realizadas después de 24, 42 y 78 horas de equilibración