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# Influence of excipients on mixtures containing high amount of dry extract from *Aesculus hippocastanum* L.

## Influência de excipientes em misturas contendo elevado teor de extrato seco de *Aesculus hippocastanum* L.

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## Abstract

The aim of this study was to evaluate the influence of the qualitative composition of excipients on formulation technology of hard gelatin capsules containing high amount of dry extract from *Aesculus hippocastanum* L. (ESAH). The rheological and technological characteristics of ESAH were determined and the influence of pharmaceutical excipients on the properties of mixtures was studied by a $2^2$ factorial design. The dissolution profiles of the capsules containing the best mixtures were obtained using sodium lauryl sulfate aqueous solution 1% (w/v) as medium. The ESAH showed high cohesivity and therefore low flow. Moreover, the ESAH showed lower level of residual moisture and was stable under controlled atmosphere. When considering pre-formulation, the filler/binder materials (microcrystalline cellulose or lactose) and glidant (colloidal silicon dioxide) increased the technological properties of the mixtures in comparison to pure ESAH. In conclusion, the dissolution profiles showed that there was no significant difference between the formulations and the ESAH, which demonstrated totally release after 30 minutes.

**Keywords:** Phytopharmaceutical. Horse chestnut seed extract. Pre-formulation. Factorial design. Solid dosage forms.

## Resumo

O objetivo deste estudo foi avaliar a influência da composição qualitativa dos excipientes na formulação de cápsulas de gelatina dura contendo alto teor de extrato seco de *Aesculus hippocastanum* L. (ESAH). As características reológicas e tecnológicas do ESAH foram determinadas e a influência dos excipientes farmacêuticos nas propriedades das misturas foi estudada por um experimento fatorial $2^2$. Os perfis de dissolução das cápsulas que contêm as melhores misturas foram obtidos utilizando uma solução aquosa

de lauril sulfato de sódio a 1 % (p/v) como meio. O ESAH mostrou alta coesividade e, portanto, baixo fluxo. Além disso, o ESAH apresentou menor nível de umidade residual e permaneceu estável sob atmosfera controlada. Ao considerar a pré-formulação, os materiais de enchimento/aglutinante (celulose microcristalina ou lactose) e de lubrificante (dióxido de silício coloidal) melhorou as propriedades tecnológicas das misturas em comparação com ESAH puro. Em conclusão, os perfis de dissolução mostraram que não houve diferença significativa entre as formulações e o ESAH, que demonstrou liberação total após 30 minutos.

**Palavras-chave:** Fitoterápico. Castanha-da-índia. Experimento fatorial. Formas farmacêuticas sólidas.

## Introduction

*Aesculus hippocastanum* L. originates from the Balkans and is cultivated in almost all of Europe and marketed worldwide. Among the main biological properties of the species, are: antiedematogenic activity (PITTLER and ERNST, 1998; SIRTORI, 2001); antiexudative and vasoprotective activity (SIRTORI, 2001) and inhibition of angiogenesis (KIM, 2003). Concerning the chemical composition, several groups are related that include flavonoids (RUTIN, QUERCITRIN and KAEMPFEROL) (HÜBNER, WRAY and NAHRSTEDT, 1999), condensed tannins (MORIMOTO, NONAKA and NISHIOCA, 1987), oils, fatty acids (BOMBARDELLI, MORAZZONI and GRIFFIN, 1996; SRIJAYANTA, RAMAN and GOODWIN, 1999) and vitamins (B, K1, C, pro-vitamin D) (BOMBARDELLI, MORAZZONI and GRIFFIN, 1996). Saponins are mainly responsible for the therapeutic properties of *A. hippocastanum* and the minimum should be 3% according to German Pharmacopoeia (DAB, 2004a, b). Also known as escins, these triterpenic saponins are a complex mixture, of which 60% consists of five substances (YOSHIKAWA et al., 1994): escin Ia (24%); escin Ib (17%); escin IIa (13.5%); escin IIb (6%) and escin IIIa (1.5%).

In recent years, the drying of plant extracts has received special attention for the development and production of solid forms. The advantages of these products can be described as: higher stability, homogeneity of constituents and easy of handling. Furthermore, the use of dried plant extracts as intermediate products for obtaining other solid forms has been a complex task. However, many of these extracts do not have the necessary properties of rheology and compressibility to allow a satisfactory process of manufacturing (SOARES et al., 2003; SOUZA et al., 2008a,b; COUTO et al., 2012). Additionally, they often show high hygroscopicity and tend to agglomerate (SOARES et al., 2005a,b; DE SOUZA et al., 2007; 2009; YATSU et al., 2016).

In this context, several alternatives have been proposed to overcome these difficulties, such as wet granulation (DE SOUZA et al., 2009; QUSAJ et al., 2012) using organic solvents and dry granulation (SOARES et al., 2005a,b; SPANIOL et al., 2009). However, the first and simpler alternative may be the use of different excipients, which can improve the rheological properties of these products (LINDEN et al., 2000; DE SOUZA et al., 2001; SOARES et al., 2005a,b).

The aim of this study was to evaluate the influence of the qualitative composition of pharmaceutical excipients on the technological properties of formulations of hard gelatin capsules containing high content of dry extract from seeds of *Aesculus hippocastanum* L.

## Material and Methods

### *Material*

Dry extract of *Aesculus hippocastanum* L. (Sanrisil, São Paulo, Brazil), sodium nitrite (Vetec, São Paulo, Brazil), colloidal silicon dioxide – CSD (Aerosil 200®, Degussa, São Paulo, Brazil), lactose (Super Tab®, FMC, USA), microcrystalline cellulose (Avicel® PH 101, FMC, USA), magnesium stearate (Bärlocher, Germany), sodium lauryl sulfate (Viafarma, São Paulo, Brazil); capsules 0 and 00 colorless (Capsulgel, São Paulo, Brazil). The excipients were used as received.

### *Methods*

*Particle size analysis by optical microscopy*

The particle analysis of *A. hippocastanum* dry extract (ESAH) was carried out by using an optical microscope equipped with nonius graduated through scale of 1 mm with 100 divisions. The mean particle size was measured through the diameter of Feret from 500 particles (n = 3). The average diameter was estimated by statistical analysis assuming a normal distribution and by using the mathematical method (DIN 66145, 1997; DE SOUZA et al., 2000; VIGNAU et al., 2000; BAUER, FRÖMMING and FÜHRER, 2012).

*Residual moisture*

The moisture of ESAH was assessed by using samples of 5.0 g and submitted to circulating air at 100 – 105 °C until constant mass (n = 5) (FB5, 2010).

*Evaluation of the stability of ESAH in controlled atmosphere*

Samples of 1.0 g of ESAH were exposed to atmospheres of 65% (RH) at room temperature. After 1, 2, 4, 6, 8, 10, 12 and 14 days of exposure, the difference in mass of samples was determined (n = 5) (DE SOUZA et al., 2000).

*Factorial Design*

The mixtures were prepared following a factorial design $2^2$, using as factors: filler/binder materials (cellulose and lactose) and lubricants/glidants (colloidal silicon dioxide and magnesium stearate). The statistic and graphic analyses were performed using STATISTICA 6.0 (StatSoft, USA) (MYERS, MONTGOMERY and ANDERSON-COOK, 2009).

*Preparation of mixtures*

The mixtures were obtained by homogenization of ESAH with the filler/binder at 100 rpm for 10 minutes. Then, the lubricant/glidant was added and the final mixing was performed for 5 minutes (Blender MixPlus®, Tepron, Brazil). Six formulations were prepared (**TABLE 1**).

*Determination of bulk and tapped densities*

Samples of 5.0 g from ESAH and mixtures I, II, III, IV, V and VI were weighed independently and carefully transferred to a 25 mL graduated cylinder and the volume of powder column was measured (bulk volume). The bulk density (bd) was established from the ratio between the mass of the sample and the bulk volume. To determine the tappet density (td), the powder column was submitted to 1250 falls using a tapping device (n = 3) (PODCZECK, 1999).

*Determination of Hausner Factor*

The Hausner Factor was established from the ratio between the compaction density and gross density of dry extract and mixtures produced according to equation 1 (HAUSNER, 1967).

$$HF = \frac{td}{bd} \quad \text{(Equation 1)}$$

where: HF = Hausner Factor, bd = bulk density (g/mL), td = tapped density (g/mL).

*Determination of the Carr Index or Compressibility*

The compressibility was established from the gross density and compaction, according to equation 2 (CARR, 1965).

$$CI = \frac{td - bd}{bd} \cdot 100 \quad \text{(Equation 2)}$$

where: CI = Carr Index; bd = bulk density (g/mL), td = compaction density (g/mL).

*Flowability*

The flow properties of the sample were estimated by the angle of repose generated by samples of 30 g using a funnel with an outflow orifice of 1.4 cm at 7 cm from the surface. The analysis was performed in triplicate and the angle was calculated from the cone formed according to equation 3 (BAUER, FRÖMMING and FÜHRER, 2012; FAHR and VOIGT, 2015).

$$\alpha = \frac{h}{r} \quad \text{(Equation 3)}$$

where: α = angle of repose, h = height of the cone, r = radius of the base.

*Capsules Dissolution*

Evaluation of dissolution conditions

The solubility of ESAH was studied in several dissolution mediums: distilled water, acid (HCl 0.1 N), phosphate buffer (pH 7.4) and aqueous solutions of sodium lauryl sulfate (0.5 to 2.5 %; w/v) (FDA, 2007). The total dissolved ESAH (DT6, Erweka, Germany) was determined by UV spectrophotometry at 270 nm (Cary 1E, Varian, Japan).

*Calibration curve for the dry extract*

250.0 mg of ESAH were transferred to the dissolution cube containing 900 mL of water (1.0% of SLS; w/v). After 60 minutes under stirring at 100 rpm and 37.5 ± 0.5 °C, the solution was filtered and diluted to concentrations ranging from 0.055 to 0.300 mg/mL. The calibration curve was fitted by linear regression using PLS method and represents the average of three curves obtained from three determinations of each concentration at 270nm.

*Dissolution Test*

The dissolution of the capsules (n = 6) was performed on a dissolution apparatus using the paddle method (DT6, Erweka, Germany). The dissolution assay was conducted in 900 mL of sodium lauryl sulfate (SLS) aqueous solutions at 1.0% (w/v) at 100 rpm. The system was maintained at 37.0 ± 0.5 ºC (FB5, 2010). The total amount of dissolved ESAH was determined at 270 nm (Cary 1E, Varian, Japan) after filtration of samples collected at: 5, 10, 15, 20, 30, 45 and 60 min.

## Results and Discussion

Seeds of *Aesculus hippocastanum* L. are used in several countries for the treatment of varicose veins and hemorrhoids. In Brazil, numerous industrial products are sold containing its extract. It is mainly marketed as seed powders, dried extracts or tablets. The technological characterization of powder beds is a crucial step in the selection of excipients that are more appropriate for the development of formulations and/or for the choice of operations used during the manufacturing process to obtain a technologically feasible final product. This approach becomes more important in highly cohesive materials such as dried extracts of plant (STRICKER, 2003; SOARES et al., 2005a,b; SPANIOL et al., 2009; RITCHEL and BAUER-BRANDL, 2011; COUTO et al., 2012).

In this context, analysis and determination of the size of the particles have a particular importance in the development of solid dosage forms. This is due to the important technological implications of packaging properties such as stability and flowability, which can lead to improper filling of dies from capsule or tablet machines causing a high variability in dose uniformity (WELLS, 1988; RITCHEL and BAUER-BRANDL, 2002; FAHR and VOIGT, 2015). The mean particle size can be estimated by several methods. The graphical and the mathematical methods are the most widely used (RITCHEL and BAUER-BRANDL, 2011; FAHR and VOIGT, 2015). Some discrepancies between procedure results have been related for the analysis of dried herbal extracts, but some correlation can be observed (DE SOUZA et al., 2000). Regarding the

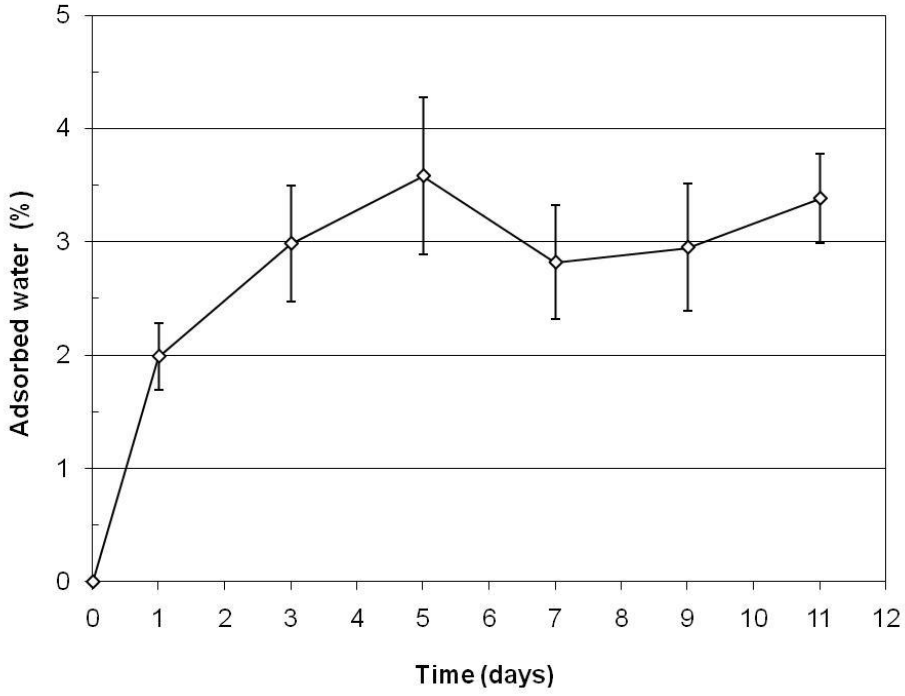
analysis of the ESAH, the estimated mean particle sizes were 9.8 µm and 12.33 µm for graphical analysis and for the mathematical method, respectively. The data suggesting that the mean particle size of ESAH stays around 10 µm. At this range of particle size, it is classified as a very fine powder. Several rheological difficulties could be expected, mainly due to interparticle interaction and lower density. Additionally, the complex and amorphous composition of dried extracts provide a higher affinity with the surrounding water vapor, improving the hygroscopic tendency (TONG et al., 2008). In this way, the residual moisture and the stability under controlled atmospheres play an important role in the formulation, development and storage of phytopharmaceuticals (SOUZA et al., 2008a; COUTO et al., 2012).

Concerning the moisture requirements for powder systems used in pharmaceutical production, the residual humidity should be lower than 8% (FAHR and VOIGT, 2015).

However, this requirement becomes more critical for products from a herbal source. Thus, due to the hygroscopic nature of their compounds, as well as the microbiological risk, the residual humidity of dried herbal products should be lower than 4% (w/w) (FB5, 2010).

Concerning our results, the dried extract of *A. hippocastanum* showed residual humidity of 9.5 ± 0.0075% (w/w), suggesting that care should be taken with packaging and storage conditions. In this way, the behavior of products under a controlled atmosphere provides a basis for the prediction of physical stability during storage, by observing physical and/or chemical changes. Regarding the preliminary studies for the ESAH performing under a controlled atmosphere of 65%, the product showed mass increases in the first 24 hours, stabilizing from the fifth day at about 4.0% (**FIGURE 1**).

**FIGURE 1.** Hygroscopic behavior of ESAH under RH of 65%.



The results show an interesting behavior for dried extract. Although the EASH presents high residual moisture, it was less sensitive to the atmospheric humidity. This data suggests an important stability of the ESAH during storage.

The determination of bulk and tapped densities is especially interesting in regards to the determination of the volume of powder column. Thus, the process performance of solid dosage forms as well as the packaging requirement can be influenced (PODCZECK, 1999).

The bulk density is a property of the powder bed and not of the individual particles. This depends on how the particles are packed, and the porosity of the powder bed. The determination of the tapped density is achieved when the powder column achieves a state of stability and the volume stays invariable. These assays are important when the powder is intended for the preparation of medicinal capsules, because the choice of appropriate capsule size will depend on the value of the apparent volume of the powder to be distributed (BAUER, FRÖMMING and FÜHRER, 2012; FAHR and VOIGT, 2015).

The ratio td/bd is related to the friction between the particles and therefore can be used to predict the flow properties of the particles. Powders of low friction between the particles show a Hausner Factor (HF) lower than 1.2, while the powders with higher cohesivity and restricted flow show HF exceeding 1.6 (HAUSNER, 1967). Regarding the compressibility index (CI), low values (< 15%) indicate materials with good compressional properties. On the other hand, materials with higher values of CI (> 25%) show poor compressibility. In this study, the HF and CI for both ESAH or mixtures were typical of powdered systems with poor flowability (SOARES et al., 2005a; RITCHEL and BAUER-BRANDL, 2011; FAHR and VOIGT, 2015).

Although the determinations of the CI and HF have been widely used for preliminary assessment of the flowability of powdered systems, the use of other methods is often report in the literature. The use of methods for measurement of flow known as dynamic procedures presents close correlations between the experimental data and the real technological characteristics of the powder. In this way, the angle of repose is a method that allows a dynamic measurement of flow by assessing the difficulty presented by the particles to flow freely through an orifice to a flat surface (PODCZECK, 1999; RITCHEL and BAUER-BRANDL, 2011; BAUER, FRÖMMING and FÜHRER, 2012). Thus, powder or granular material flows through the orifice and generates a cone at the surface. The angle of the base of the cone is known as the angle of repose. This definition was introduced by Dallavalle (1948), and systems which show angles of repose higher than 30° are typical of those with resistance to flow. The results observed for the materials showed a system with high difficulty to flow (**TABLE 1**).

Regarding the formulations employed to perform the factorial design, it could be observed that the combination of ESAH with filler/binder materials and lubricants/glidants changed the technological properties of the systems. Thus, the rheological properties of the mixtures were improved and the statistical analyses denote the improvement of the rheological parameters (HF, CI and angle of repose). Therefore, significant influence could be attributed to the following conditions: interaction between factors for the HF response, as well as the type of lubricant/glidant for the angle of repose (**TABLE 2**).

**TABLE 1** - Composition and rheological parameters of the dry extract of *A. hippocastanum* (ESAH) and respective mixtures.

| Sample | EXTRACT (%) | FBM (%) | LUB/GLI (%) | bd | td | HF | CI (%) | α |
|---|---|---|---|---|---|---|---|---|
| ESAH | 100.0 | 0.0 | 0.0 | 0.34 ± 0.01 | 0.53 ± 0.01 | 1.55 ± 0.08 | 35.40 ± 3.10 | 44.2 ± 0.22 |
| Mixture I | 50.0 | 49.5 (Lactose) | 0.5 (CSD) | 0.44 ± 0.01 | 0.65 ± 0.05 | 1.46 ± 0.02 | 31.42 ± 1.27 | 43.2 ± 0.63 |
| Mixture II | 50.0 | 49.5 (Lactose) | 0.5 (Mg-Stearate) | 0.42 ± 0.04 | 0.64 ± 0.01 | 1.55 ± 0.12 | 34.90 ± 4.89 | 47.0 ± 1.33 |
| Mixture III | 50.0 | 49.5 (Cellulose) | 0.5 (CSD) | 0.36 ± 0.01 | 0.50 ± 0.02 | 1.40 ± 0.01 | 28.47 ± 0.67 | 44.0 ± 0.33 |
| Mixture IV | 50.0 | 49.5 (Cellulose) | 0.5 (Mg-Stearate) | 0.36 ± 0.01 | 0.53 ± 0.01 | 1.46 ± 0.01 | 31.65 ± 0.70 | 45.4 ± 1.97 |
| Mixture V* | 50.0 | 49.5 (Lactose) | 0.5 (CSD) | 0.44 ± 0.01 | 0.61 ± 0.01 | 1.40 ± 0.04 | 28.80 ± 1.72 | 43.5 ± 0.67 |
| Mixture VI* | 50.0 | 49.5 (Cellulose) | 0.5 (CSD) | 0.35 ± 0.02 | 0.47 ± 0.01 | 1.35 ± 0.04 | 26.08 ± 2.11 | 43.5 ± 1.00 |

*Additional mixtures to extend the experimental field;

FBM = filler/binder materials. LUB/GLI = lubricants/glidants; bd = bulk density; tp = tapped density; HF = Hausner Factor; CI = Carr index; α = repose angle.

**TABLE 2** - ANOVA analysis for formulation excipients from $2^2$ factorial design.

| Source of variation | $F_{(HF)}$ | $F_{(CI\%)}$ | $F_{(\alpha)}$ |
|---|---|---|---|
| FBM (1) | 1.92 | 3.60 | 0.01 |
| LUB/GLI (2) | 1.28 | 4.50 | 18.42* |
| Interaction (1by2) | 13.35* | 1.10 | 4.55 |

* Significant for α = 0.05;

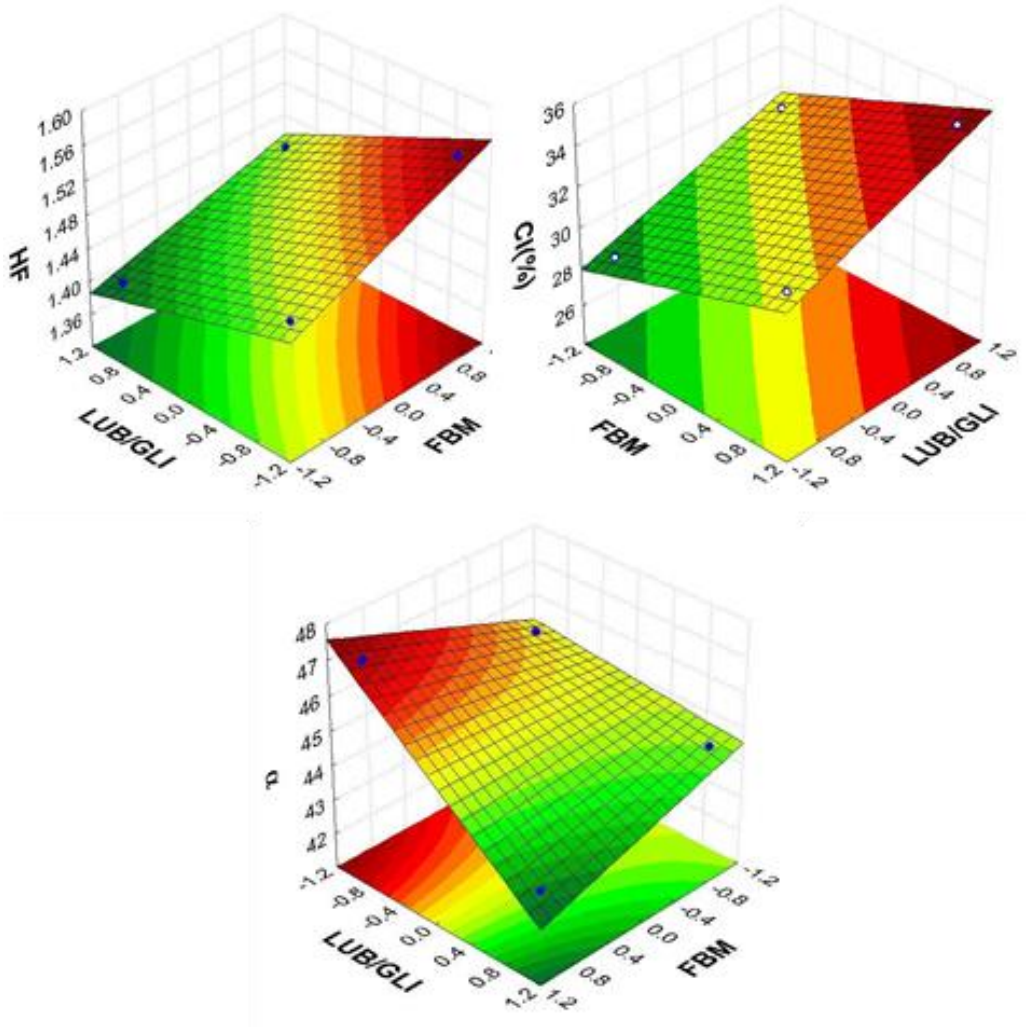
FBM = filler/binder materials. LUB/GLI = lubricants/glidants; HF = Hausner Factor; CI = Carr index; α = repose angle.

Concerning the complex and multifactorial nature of the rheological properties of powder bulk, such as inter-particle interaction, the powder flow can be disturbed as a result of incomplete or irregular flow patterns.

Due to the typical intrinsic variability of such experiments, the results for the statistical analysis often cannot completely reflect the phenomenon that is happening during the determinations. In other words, it is not totally able to detect and clarify the majority of the phenomena. In fact, the statistical approaches by hypothesis tests allow us to identify and quantify the major factors or level set-ups crucial to a determined response. However, in cases like pre-formulation studies, where a continued nature should be taken into account, a graphic approach plays an important role in clarifying and understanding the physical and technological behavior during the formulation processes, such as the contribution of each factor, their combinations and levels, as well as the mathematical order followed.

In this context, the use of response surfaces can measure the tendency of the behavior of certain input variables on certain answers. The areas corresponding to the Hausner Factor (HF), Compressibility Index (CI%) and angle of repose (α), are represented in (**FIGURE 2**).

**FIGURE 2** - Response surfaces for: Hausner Factor (HF), Compressibility Index (CI%) and angle of repose (α). FBM = filler/binder materials. LUB/GLI = lubricants/glidants.




The overlap of areas suggests that the combination with the best conditions for preparation of the formulations contain dry extract of *A. hippocastanum* including CSD as glidant. To confirm the influence of this excipient, two other experiments were performed with higher concentrations in the presence of both filler/binder materials (**TABLES 1 and 3**).

**TABLE 3 -** Results of the $2^2$ factorial design.

| Exp. | FBM | LUB/GLID | HF | | AR | |
|---|---|---|---|---|---|---|
| | | | 0.5% | 1% | 0.5% | 1% |
| 1 | L (–) | AER (–) | 1.47 | 1.40 | 43.2 | 43.5 |
| 2 | L (–) | Mg S (+) | 1.55 | – | 47.0 | – |
| 3 | CMC (+) | AER (–) | 1.40 | 1.35 | 44.5 | 43.5 |
| 4 | CMC (+) | Mg-St (+) | 1.46 | – | 45.3 | – |

Exp.: Experiment; FBM = filler/binder materials; LUB/GLI = lubricants/glidants; L: Lactose; CMC: Cellulose Microcrystalline; AER: Aerosil; Mg-St: Mg-Stearate.

The rheological evaluation by Compressibility Index and Hausner Factor suggested that the mixtures containing colloidal silicon dioxide (V and VI), which showed lower angles of repose, also exhibited better flow properties. On the other hand, the mixtures containing magnesium stearate (II and IV) showed the largest angle of repose and probably the worst behavior of flow.

Regarding the contribution of each excipient, the influence of the CSD as a glidant enabled a decrease in the Hausner Factor and the angle of repose for both filling materials. In fact, the small spherical CSD agglomerates adhere to the surface of filler/binder material and reduce the attraction forces between particles, increasing the roller friction in comparison to sliding friction. This behavior can explains the better flow performance to mixtures containing CSD than other mixtures containing magnesium stearate. Additionally, hydrophobic lubricants such as magnesium stearate are able to forming capable of forming films on other excipients during mixing, decrease the solubility and prolonging the active liberation (PODCZECK, 1999; BAUER, FRÖMMING and FÜHRER, 2012; HURTADO et al., 2012; FAHR and VOIGT, 2015).

Orally administered drugs must be dissolved or in solution before they can be absorbed. Lower soluble molecules are solubilized in the gastro-intestinal tract by endogenous surfactants such as bile acids, bile salts, lecithins and so on, before they are absorbed (JONAT et al., 2004). *In vitro* tests using acids/bile salts showed an increase in the dissolution of poorly soluble drugs as the concentration of surfactant increases (KWAN et al., 1977; SHAH et al., 1989). However, due to the high cost of these substances, their use in routine testing of dissolution is impractical. Thus, the use of synthetic surfactants as an alternative has been frequently used in the routine. In this way, the surfactants Tween 80 and SLS have been widely used in order to promote the dissolution of poorly soluble molecules (SHAH et al., 1995; JAMZAD and FASSIHI, 2006).

However, as is well known, the dissolution of drugs is the result of the release of the molecule in the medium of dissolution. In this context, the diffusivity of dissolved specimens (drug molecules and complex molecule-micelle) plays an important role (JAMZAD and FASSIHI, 2006). The diffusivity of the complex drug-micelle is smaller than the molecule itself and change in the rate of dissolution is a result of an increase in solubility plus the decrease in diffusivity (CRISON et al., 1996; BALAKRISHNAN et al., 2004; JAMZAD and FASSIHI, 2006). Due to the high molecular weight of Tween 80 and the great mass of its aggregation micelles in comparison with SLS (TURRO and YEKTA, 1978; NERURKAR et al., 1997; JAMZAD and FASSIHI, 2006), the polysorbate provides low diffusivity of the complex drug-micelle and consequently reduces the rate of dissolution (BALAKRISHNAN et al., 2004; JAMZAD and FASSIHI, 2006). Therefore, the use of SLS is recommended by several official codes to study dissolution behavior of poor soluble molecules.

Thus, due to the low solubility of Escins (saponins from *A. hippocastanum*), the SLS was used as surfactant to perform the *in vitro* study. However, in order to quantify the release, the total ESAH was considered as the active principle. Therefore, it was assumed that its release represents the total release of all constituents of interest (DE SOUZA et al., 2001).

The data for the preliminary assessment of the release profile in different mediums from hard capsules containing the ESAH (250 mg) by using the paddle method at 100 rpm are shown in (**TABLE 4**). The results showed the low ability for total release of ESAH in pure water, acid or base. On the other hand, the release of ESAH was made possible by using SLS solutions as medium. The release was improved significantly and the

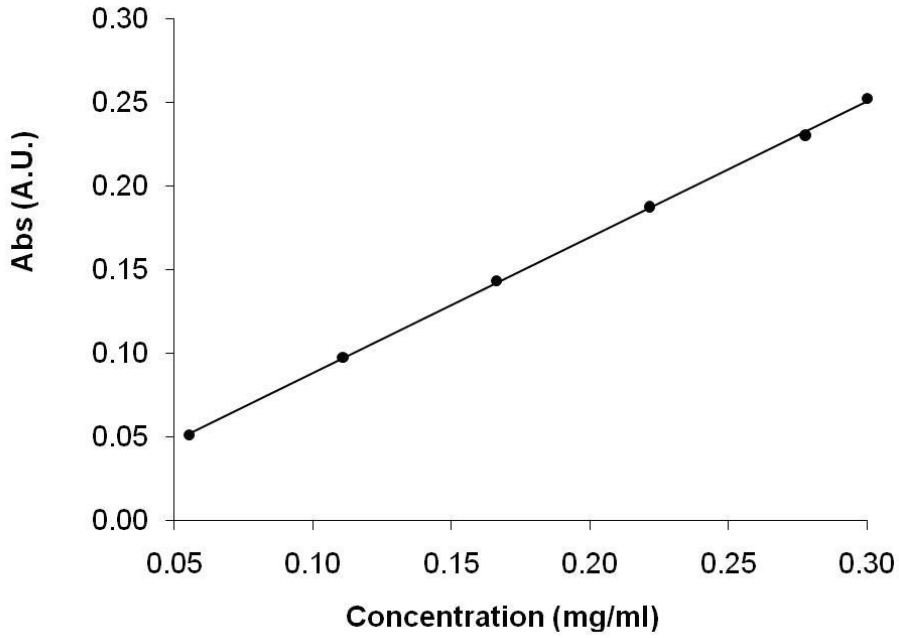
maximum performances were recorded at concentrations of SLS between 0.5 and 1.5 % (w/v). In this way, the medium containing SLS 1.0 % (w/v) was adopted as a release medium for capsules containing ESAH.

**TABLE 4 -** Preliminary assessment of dissolution for capsules containing the ESAH.

| Method of dissolution | Abs (U.A.) | ESAH released (%) |
|---|---|---|
| Water | 0.3165 | 63.89 |
| HCl 0.1 N | 0.0831 | 16.77 |
| Phosphate buffer (pH = 7.4) | 0.2480 | 50.06 |
| SLS 0.5% | 0.4918 | 99.27 |
| SLS 1.0% | 0.5150 | 103.96 |
| SLS 1.5% | 0.4954 | 100.00 |
| SLS 2.0% | 0.4730 | 95.48 |
| SLS 2.5% | 0.4620 | 93.26 |

The total release of ESAH in the medium was calculated by a calibration curve evaluated at concentrations ranging in accordance with experimental dissolution conditions. The curve was described by the equation y = 0.8142 x + 0.0071 and the determination coefficient ($R^2$) was 0.9997, indicating that the equation describes satisfactorily the experimental variance in the laboratorial conditions (**FIGURE 3**).

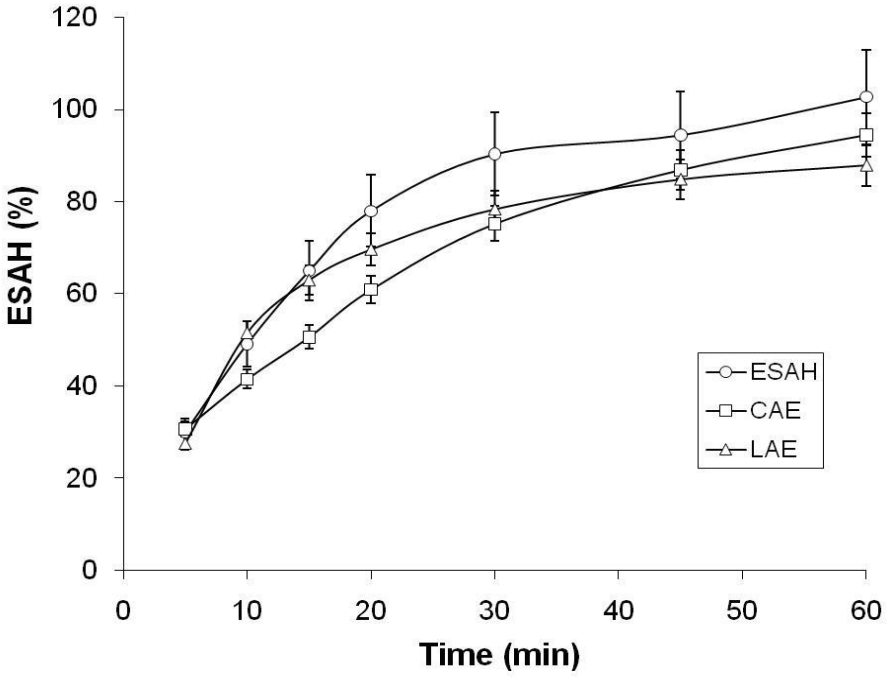
**FIGURE 3 -** Calibration curve for the dry extract of *A. hippocastanum*.




The dissolution data showed similar profiles for the three batches tested: pure extract, formulations V and VI. Overall, maximum release of ESAH was achieved after 30 minutes (**FIGURE 4**). The capsules containing pure ESAH showed a slight increase in the released concentrations. However, no technological difference could be attributed to this behavior. Both formulations also showed similar profiles, but due to the solubility of the filler material, formulation containing lactose as filler presented faster release in the first minutes. The

slight variations observed between release profiles of formulations were not great enough and could be the result of the variability resulting from technological properties of the mixtures.

**FIGURE 4 -** Dissolution of capsules containing dried extract. ESAH: Dried extract of *A. hippocastanum* (○); CAE: Cellulose-Aerosil-Extract mixture (□); LAE: Lactose-Aerosil-Extract mixture (△).




## Conclusions

The technological characteristics of dry extract from *A. hippocastanum* revealed that it has some promising properties (such as low residual moisture and stability in a humid atmosphere), which could support its use as an intermediary product for manufacture of solid dosage forms. On the other hand, the rheological properties of the particulate bed showed limited application for the development of solid dosage forms such as capsules and tablets. Furthermore, the system has characteristics that will not encourage its use in processes that depend on flow and compressibility. However, the use of excipients such as cellulose/lactose and colloidal silicon dioxide provide significant improvements on the extract properties, demonstrating its feasibility for production of solid dosage forms. Finally, the dissolution test developed in this work showed that the total release of the *A. hippocastanum* dry extract from hard gelatin capsules was possible only with the use of surfactant. This, there was no significant difference between the release profiles of pure extract and formulations studied.

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