Preparation and characterization of solid oral dosage forms containing soy isoflavones

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Abstract: Soy isoflavones have been extensively used for menopausal symptoms and prevention of hormone-related cancer, osteoporosis and cardiovascular diseases. Commercially available forms of isoflavones include supplements, capsules and tablets. However, the non-standardization of soy isoflavones extracts and different dissolution profiles of these solid dosage forms highlight the need of additional studies on the development of well characterized pharmaceutical dosage forms of isoflavones. In this work, immediate release oral tablets of soy isoflavones were obtained and evaluated. Genistein and daidzein, were the main constituents of the dried soy extract. Preparation of the tables was accomplished in a rotary tableting machine following either a dry mixture for direct compression or wet granulation with different excipients. Powder, granules and tablets were evaluated for several parameters, including flow properties, Carr and Hausner indexes, hardness, friability, disintegration time and drug release profile. Also, a fast and validated HPLC analytical method for both genistein and daidzein was developed. Formulations containing sodium croscarmellose and sodium dodecyl sulfate resulted in better flowability as indicated by the flow rate and angle of repose, faster disintegration time and immediate release dissolution profile.

Keywords: daidzein dissolution genistein HPLC isoflavone extract tablets

Introduction

Scientific developments have increased the interest in the use of herbal products as therapeutic agents (Silva et al., 2012). From a vast number of plant constituents, isoflavones are among the most studied due to their estrogen-like activity without common side effects from hormonal therapies (César et al., 2006). Additionally, isoflavones have been extensively used for menopausal symptoms and prevention of hormone-related cancer, osteoporosis and cardiovascular diseases (Howes et al., 2000; Ferrari, 2009).

Isoflavones have been widely used and became commercially available as over-the-counter (OTC) supplements, capsules and tablets. The extensive advantages of oral dosage forms, such as convenience and compliance, made isoflavone tablets very popular for postmenopausal treatments (Shen et al., 2010). However, the development of solid dosage forms using plant raw materials is not an easy task since herbal materials exhibit poor flowability and low compressibility (Palma et al., 2002). In addition, isoflavones most frequently found in soybean extracts (genistein, daidzein, genistin, daidzin and glycitin) are poorly water-soluble with low membrane permeability, which is considered a challenge for the development of oral dosage forms (Shen et al., 2010).

Clinical trials with the commercial dosage forms containing isoflavones demonstrated a large variability of therapeutic and side effects originated from these preparations, questioning the reliability of the efficacy and safety of these phytomedicines (Palma et al., 2002). These variations could be caused mainly by the non-standardization of soy isoflavones extracts (Setchell et al., 2005; Campos et al., 2006) and different dissolution profiles of the solid dosage forms.

In spite of the wide use isoflavones as phytomedicines, few studies related to the development of isoflavone tablets have been conducted. Until recently, the majority of the concerns have been focused on the standardization extract, but little attention has been given to the development of pharmaceutical forms. In the present work, a systematic investigation of formulation and technological parameters on soy isoflavone tablets was performed. Tablets with different disintegrating agents, surfactants and diluents were obtained either by direct compression or wet granulation, and the influence of these techniques was evaluated.
Additionally, an analytical method for genistein and daidzein was developed and validated according to ICH guidelines in order to monitor the quality of the tablets, their stability and dissolution profile for these main constituents of the soybean extract.

Materials and Methods

Materials

Dried soy extracts (≥40% of total isoflavones) were produced by Sichuan Xieli Pharmaceutical (China) and distributed by PharmaNostra (Anápolis, Brazil, batch number 08010079A). According to the manufacturer, the total content of the glycosides daidzin and genistin was, combined, 3.25% (w/w). Daidzein and genistein content were 32.79% (w/w) and 10.75% (w/w), respectively. Analytical standards daidzein and genistin was, combined, 3.25% (w/w) were purchased from LC Laboratories (Woburn, MA, USA). Microcrystalline cellulose PH-102 and sodium croscarmellose (CROS) were purchased from Blanver Farmoquímica Ltda (São Paulo, Brazil). Crospovidone (CROS-POV) (Polyplasdone XL®, particle size 100-130 µm and Polyplasdone XL-10, particle size 30-50 µm) was kindly donated by ISP (São Paulo, Brazil). Hydroxypropyl methylcellulose (Opadry YS-1-7006®) was purchased from Colorcon Inc. (São Paulo, Brazil). Titanium dioxide was from Huntsman (California, USA). Magnesium stearate was from Shenzhou Light Ind. Factory (China). Talc, anhydrous dicalcium phosphate and lactose M200 were from Indukern (Barcelona, Spain). Colloidal silicon dioxide was purchased from Evonik Industrie (Germany). Sodium dodecyl sulfate (SDS) was purchased from Vetec (São Paulo, Brazil). Acetoinitrile, methanol, and acetic acid were HPLC grade and were purchased from JT Baker (Phillipsburg, NJ, USA). Water was purified using a Milli-Q system (Millipore®, Billerica, MA, USA) with a 0.22 µm pore end filter.

Methods

Genistein and daidzein quantitation by High Performance Liquid Chromatography

Chromatographic separation of genistein and daidzein was achieved with an HPLC system consisting of a quaternary pump (ProStar 240, Varian, Palo Alto, CA, USA), autosampler (ProStar 410, Varian, Palo Alto, CA, USA) and UV detector (ProStar 310, Varian, Palo Alto, CA, USA). Separation was achieved in an Agilent ChromSpher C18 column (150 x 4.6 mm, 5 µm) with column temperature of 30 °C. The mobile phase was methanol (0.1% acetic acid):water (0.1% acetic acid):acetonitrile 64:32:4 (v/v/v). Flow-rate was 0.7 mL/min, injection volume was 10 µL and UV detection was carried out at 254 nm. Data acquisition was performed using a Galaxie Chromatography Data System Software. The method was validated in accordance to ICH guidelines (ICH, 2003).

Analysis of dried soy extract

Samples of dried soy extract were analyzed using the validated HPLC method described above. The amount of genistein and daidzein was determined without previous acidic hydrolysis. Ten milligrams of dried soy extract were weighted and added to a volumetric flask with 50 mL methanol. The solution was sonicated for 20 min, diluted to obtain a final concentration of 100 µg/mL, filtered and analyzed by HPLC.

For the hydrolysis procedure, 50 mg of dried soy extract were mixed with 3.0 M HCl ethanolic solution in a volumetric flask (100 mL). The mixture was heated (60 °C) and refluxed for 40 min. After that, samples were diluted to obtain a final concentration of 100 µg/mL, filtered and analyzed by HPLC.

Development of solid dosage forms containing dried soy extract

Tables containing dried soy extract were produced by either wet granulation or direct compression techniques. Table 1 shows the percent composition of the tablets prepared with soy extract. The influence of the type and concentration of the disintegrant agent, as well as the presence of the surfactant were determined for the wet granulation formulations (Table 1). The granulation was achieved by mixing the plant extract and the adjuvants previously sieved (sieve aperture 1.0 mm); then, 300 g of the resulting mixture were agglomerated by adding 90 mL of an ethanolic solution containing povidone 3% (w/v). After the addition of the liquid, the wet mass was passed through a 2 mm sieve in a conical mill (Stinfer, model GS Lab, São Paulo, Brazil). The granules were dried in an oven at 40 °C until the relative humidity reached 5% (w/w). After that, dry granules were calibrated in a 1.4 mm sieve and mixed with colloidal silicon dioxide (0.5%) and magnesium stearate (1.5%) using a V-mixer for 5 min at 10 rpm. A rotary tablet machine (Lawes model 08-PSC MANU, São Bernardo do Campo, Brazil) was fed with this final mixture and circular tablets (9 mm width) with 300 mg weight were obtained.

For the preparation of tablets by direct compression (DC), mixtures of dried soy extract (50%) with the adjuvants (Table 1) were obtained in a V-mixer (10 min at 10 rpm). Blends were directly compressed on a rotary tablet machine (Lawes model 08-PSC MANU,
Preparation and characterization of solid oral dosage forms containing soy isoflavones

São Bernardo do Campo, Brazil) using 9 mm circular punches and dyes.

Tablet coating

Tablets were coated using a conventional pan coater (Lawes, São Bernardo do Campo, Brazil) and a two-fluid coaxial type atomization device (DeVilbiss, Glendale Heights, USA) with an insert diameter of 1.4 mm. The coating suspension was prepared by dissolving the 3.0% (w/v) hydroxypropyl methylcellulose (Opadry® YS-1-7006), 1.0% (w/v) polyethylene glycol 6,000, 2.0% (w/v) titanium dioxide and talc and 0.05% (w/v) red dye. Five hundred milliliters of the ethanolic dispersion were applied to the tablets’ surface after tablet bed temperature reached 40 °C by insufflation of heated air.

Characterization of powder and granules

The flowability of soy isoflavone extract, powder mixtures and granules was characterized by measuring flow rate (Erweka GTB, Frankfurt, Germany), angle of repose (Erweka GTB, Frankfurt, Germany), Carr and Hausner indexes.

Flow rate and angle of repose were determined by pouring 100 g of the sample through a funnel (15 mm diameter orifice). Automatic measurement of flow rate was obtained in an Erweka GTB instrument. Angle of repose was determined by measuring the slope of the heap of powders or granules that fell from the funnel to a flat surface.

Carr and Hausner indexes were determined from tapped and bulk density data. Bulk density was determined by adding 100 g of powder to a graduated cylinder (250 mL). Tapped density was measured after tapping 500 times the cylinder (Erweka SVM 203, Frankfurt, Germany) according to USP 35. Equations 1 and 2 were employed to calculate Carr and Hausner indices:

\[
\text{Carr index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100
\]

\[
\text{Hausner index} = \frac{\text{tapped density}}{\text{bulk density}}
\]

Water content of the powder and granules was gravimetrically determined using an infrared scale (Gehaka, São Paulo, Brazil). Soy extract, powder mixture or granules were added to the scale plate and dried at 105 °C until constant weight.

Characterization of tablets containing dried soy extract

The physical properties of the tablets were evaluated according to the 4th edition of the Brazilian Pharmacopeia (1988). To study weight variation, twenty tablets of each formulation were weighed using an electronic scale (Sartorius digital balance TE-214S, NY, USA). Thickness and hardness were measured individually from twenty tablets using a portable digital tablet tester (Nova Ética, model 298 DGP, Vargem Grande Paulista, Brazil). Friability was determined from twenty tablets by measuring the average weight lost after 100 revolutions in a friabilometer (model 300.1, NOVA ÉTICA, São Paulo, Brazil). Disintegration was determined in a disintegration apparatus (model 301/AC, NOVA ÉTICA, São Paulo, Brazil), with a water bath operating at 37±1 °C. Six tablets were individually placed in the apparatus cylinders. Disintegration time was recorded when the last of the six units was completely disintegrated.

In vitro drug release studies (Dissolution test)

To properly design the dissolution assay, genistein and daidzein solubilities were evaluated in several different media: water, sodium acetate buffer

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Lactose a</th>
<th>Dicalcium phosphate a</th>
<th>Sodium croscarmellose (CROS) b</th>
<th>Crospovidone (CROS-POV) XL c</th>
<th>Crospovidone (CROS-POV) XL-10 c</th>
<th>Sodium dodecyl sulfate (SDS) d</th>
<th>Colloidal silicon dioxide e</th>
</tr>
</thead>
<tbody>
<tr>
<td>CROS</td>
<td>26.98</td>
<td>-</td>
<td>3.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.50</td>
</tr>
<tr>
<td>CROS-SDS</td>
<td>24.98</td>
<td>-</td>
<td>3.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.00</td>
</tr>
<tr>
<td>CROS-POV</td>
<td>25.98</td>
<td>-</td>
<td>2.00</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.00</td>
</tr>
<tr>
<td>CROS-POV-10</td>
<td>25.98</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.00</td>
<td>-</td>
<td>2.00</td>
</tr>
<tr>
<td>DC</td>
<td>29.98</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
</tbody>
</table>

The other components were added to all formulations in the same amounts (soy extract (50%), diluent microcrystalline cellulose (15%), lubricant magnesium stearate (1.5%) and antioxidant butylhydroxytoluene (0.02%)); b diluent; c disintegrant; d surfactant; e lubricant.
Preparation and characterization of solid oral dosage forms containing soy isoflavones

Stela R. de Oliveira et al.

(SAB) pH 4.5, water+3% SDS, water+3% polysorbate 80, water+3% polysorbate 20. Fifty miligrams of soy extract were added to 50 mL of each medium. Vessels were kept at 37±0.5 °C and stirred at 150 rpm. After 24 h, 2 mL samples were withdrawn, centrifuged at 1620 x g, filtered and quantified by HPLC.

Dissolution profiles for genistein and daidzein from different tablets were evaluated by using 900 mL of 3% SDS aqueous solution in a Varian VK 7000 Dissolution Test System (Cary, USA) equipped with paddle apparatus (USP Apparatus 2) kept at 37±0.5 °C. Samples were stirred at 100 rpm for 120 min and, after that, stirring was raised to 150 rpm to reach dissolution infinite point. Samples of 3 mL were collected at 5, 10, 15, 30, 45, 60, 90, 120 and 150 min, filtered and quantified by HPLC. All analyses were performed under sink conditions (n=6). Data were analyzed using ANOVA with p<0.05 as the minimal level of significance.

Results and discussion

Several studies have reported the quantitation of soy isoflavones by HPLC (Apers et al., 2004; César et al., 2006; César et al., 2007; Prabhakaran et al., 2006). The method reported here was adapted from the literature and validated in accordance to ICH guidelines. The chromatographic conditions employed resulted in a faster elution of genistein and daidzein (3.29 and 3.97 min, respectively) compared to other literature methods (Apers et al., 2004; César et al., 2006; César et al., 2007). Figure 1 illustrates a chromatogram obtained for genistein and daidzein quantitation according to the analytical method. Tail factor was 1.15 and 1.12 for genistein and daidzein, respectively. Theoretical plate values were above 2000 for both isoflavones, demonstrating peak symmetry. The calibration curve was linear in the concentration range (1.5-36 µg/mL) for both genistein (y=0.0148x-0.0341, r=0.9998) and daidzein (y=0.0145x-0.0481, r=0.9999).

Precision and accuracy were determined from solutions at concentrations of 1.5, 15 and 30 µg/mL of genistein or daidzein with variation coefficients always lower than 5%. Intra- and inter-day precision and accuracy of the method for daidzein varied from 0.58 to 4.68% and 97.27 to 102.44%, respectively. For genistein, intra- and inter-day precision and accuracy varied from 0.34 to 1.67% and 96.40 to 99.56%, respectively. The limit of quantitation for both genistein and daidzein was 0.08 µg/mL. The selectivity was investigated against tablets components and dissolution medium. No interference was observed in the genistein and daidzein retention time, indicating the specificity of the proposed method (Figure 1). The method was validated in accordance to the ICH guidelines (2003).

The amount of genistein and daidzein in the dried soy extract was then determined. Soy extract had 27.8±1.25% (w/w) of daidzein and 11.1±0.7% (w/w) of genistein, slightly different from the information given by the manufacturer, as previously reported. The glycosides daidizin and genistin were not detected. The aglycone concentrations after acidic hydrolysis of soy extract were very similar (p>0.05) to the concentrations in the hydrolyzed samples (27.5±0.2% for daidzein and 11.0±0.1% for genistein). These small differences indicate that the method proposed in this study for a fast and reliable determination of genistein and daidzein was applicable even without the need for a prior hydrolytic step.

Development of solid dosage forms containing dried soy extract

Improving the quality of solid dosage forms obtained from plant extracts has been the focus of an increasing number of studies, and the use of suitable excipients or wet granulation techniques has demonstrated great potential in improving the performance of these formulations (Gallo et al., 2011). Properties of the soy extract in powder or in granular forms are shown in Table 2. Pure dried soy extract didn’t flow through a 15 mm diameter orifice in the GTB flow tester. Carr and Hausner indexes, as well as angle of repose values, indicate a high cohesiveness for pure dried soy extract, which is an undesirable feature for the use in direct compression process (Patra et al., 2008; Palma et al., 2002). Similarly, the formulation designed for direct compression prepared with 50% (w/w) of soy extract (DC, Table 2) also resulted in high values for Carr and Hausner indexes, denoting still a high cohesiveness of the mixture. A slight improvement of the flow properties was obtained with this formulation; however, the flow rate was still inadequate for the
necessary tableting technological parameters.

Granules prepared by wet granulation exhibited a marked improvement in flowability. Table 2 exhibits the flow properties and scale of flowability of the soy extract and its formulations according to USP35. Based on the values for angle of repose, Carr and Hausner indexes, formulations CROS-SDS and CROS-POV presented a better flow performance in comparison with the other formulations. It can be noticed that the granules with the poorest flow were prepared without SDS (granules CROS, Table 2). Most of the formulations had water content in the range of 4.5 to 5.0%. However, formulations prepared without SDS (CROS and DC, Table 2) showed a lower level of residual water. These findings suggested the influence of the surfactant on water uptake and granule density, which might interfere in the flow properties of the material.

Table 3 presents data on the characterization of tablets obtained according to formulations described in Table 1. No significant differences were observed in results for average weight, hardness and thickness of all tablets. Tablets prepared by direct compression showed a higher friability, which was significantly different from other formulations, but within the pharmacopeial specifications. Differences were also observed in the disintegration time of the tablets. Tablets containing croscarmellose and prepared without SDS showed disintegration times similar to the tablets prepared with crospovidone (≈23 min). On the other hand, croscarmellose tablets containing SDS showed a faster disintegration, probably due to the increase on the wetting properties of the tablets due to the presence of the surfactant.

Solubility of genistein and daidzein in water with 3% of SDS were determined to be 825 µg/mL and 250 µg/mL, respectively, which allowed for the dissolution study to be conducted under sink conditions, defined as the media volume at least three times higher than the necessary to obtain a saturated solution of the drug (Farmacopéia Brasileira, 1988). Tablets obtained in this study were prepared with 150 mg of dried soy extract, containing 11.1% of genistein and 27.8% of daidzein. Drug release assay was conducted with a dissolution medium of 900 mL, in which the maximum concentration of isoflavones would be around 18.5 µg/mL for genistein and 46 µg/mL for daidzein. These maximum theoretical concentrations are, respectively, 5.4 and 45 times lower than the amount dissolved in the media containing SDS, ensuring the sink conditions of the assay.

The in vitro release profiles of genistein and daidzein from the different tablet formulations are shown in Figure 2. Genistein release (Figure 2a) from the tablet prepared with sodium croscarmellose as disintegrant (CROS-SDS) was faster than drug release from the other formulations in the first 45 min of experiment. Daidzein release from CROS-SDS and the other formulations was statistically different (p<0.05) from 15 to 30 min of the drug release assay. This finding is in agreement with disintegration data (Table 3). The polymeric coating used in this work (HPMC) is a water-soluble film-forming agent used for the manufacture of immediate-release solid dosage forms. There were no differences in the drug dissolution rate from coated and non-coated tablets (data not shown). The polymeric coat used in this work was intended to promote specific benefits such as improving the visual qualities of the dosage form, masking unpleasant organoleptic properties and easing ingestion of the tablets.

The best mathematical fit for the drug release data describes a zero order kinetics model and the calculated constant rate value (k) was higher for the CROS-SDS formulation (Table 4). CROS formulation was also prepared with croscarmellose, however, its disintegration and genistein release profile were similar to the formulations prepared with crospovidone and SDS (p>0.05). In spite of this, the k value for croscarmellose formulations was higher than the calculated k for crospovidone formulations. This behavior can be attributed to the lower wetting of the CROS tablets due to absence of the surfactant, which also increased the disintegration time.

<table>
<thead>
<tr>
<th>Material</th>
<th>Flow rate (s)</th>
<th>Angle of repose (°)</th>
<th>Carr index</th>
<th>Hausner index</th>
<th>Water content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy isoflavone extract (powdered form)</td>
<td>-</td>
<td>-</td>
<td>42.86f</td>
<td>1.75f</td>
<td>4.4±0.2</td>
</tr>
<tr>
<td>Granules CROS-SDSa</td>
<td>4.8±0.8</td>
<td>28.4±0.5</td>
<td>18.68</td>
<td>1.23</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>Granules CROSa</td>
<td>6.7±0.9</td>
<td>34.1±1.8</td>
<td>26.06</td>
<td>1.35</td>
<td>2.7±0.2</td>
</tr>
<tr>
<td>Granules CROS-POV-10a</td>
<td>4.8±1.1</td>
<td>28.3±1.2</td>
<td>22.45</td>
<td>1.29</td>
<td>5.0±0.1</td>
</tr>
<tr>
<td>Granules CROS-POVb</td>
<td>4.5±0.5</td>
<td>27.6±0.9</td>
<td>16.85</td>
<td>1.20</td>
<td>4.9±0.2</td>
</tr>
<tr>
<td>DC powdered form</td>
<td>50.6±2.8</td>
<td>39.2±1.1</td>
<td>40.00</td>
<td>1.66</td>
<td>2.3±0.3</td>
</tr>
</tbody>
</table>

1Formulations from Table 1; low properties and corresponding angles of repose, according to USP 35: *excellent; †good; ‡fair; Scale of flowability based on Carr and Hausner indexes, according to USP35: †very, very poor; ‡fair; ‡poor; †passable.
Preparation and characterization of solid oral dosage forms containing soy isoflavones

Stela R. de Oliveira et al.

The type of crospovidone used did not promote changes neither in disintegration nor genistein release form soy tablets. Polyplasdone XL and Polyplasdone XL-10 differ by the size of the crospovidone particles. Polyplasdone XL has a larger particle size (100-130 µm) and should provide a faster disintegration time than Polyplasdone XL-10 (30-50 µm particle size). In the present work, the particle size did not alter disintegration and in vitro drug release of genistein.

The best mathematical fit of daidzein release data also described azero order kinetics and exhibited the same tendencies observed for genistein. Statistical differences between CROS-SDS formulation and the other tablets were only seen in the first 30 min of the assay.

The CROS-SDS tablet formulation presented the higher k values for genistein and daidzein and the release amounts were significantly higher for this composition. Based on the characteristics of immediate release pharmaceutical tablets, CROS-SDS can be considered as the most appropriated formulation in this study.

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References


Campos MG, Paranhos AH, Matos MP, Câmara MT, Cunha

Table 3. Characterization of tablets prepared by wet granulation or direct compression.

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Average weight (mg)a</th>
<th>Hardness (Kgf)b</th>
<th>Thickness (mm)c</th>
<th>Disintegration (min)d</th>
<th>Friability (%)e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet CROS-SDS</td>
<td>301.5±3.7</td>
<td>9.4±1.5</td>
<td>4.65±0.02</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Tablet CROS</td>
<td>306.8±2.3</td>
<td>8.2±2.1</td>
<td>5.10±0.06</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Tablet CROS-POV-10</td>
<td>298.7±4.6</td>
<td>10.1±1.6</td>
<td>4.59±0.02</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Tablet CROS-POV</td>
<td>301.4±3.3</td>
<td>9.2±0.8</td>
<td>4.67±0.07</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Tablet DC</td>
<td>314.9±15.7</td>
<td>9.1±5.2</td>
<td>5.02±0.23</td>
<td>16</td>
<td>0.5</td>
</tr>
<tr>
<td>DC powdered forma</td>
<td>50.6±2.8</td>
<td>39.2±1.1</td>
<td>40.00</td>
<td>1.66e</td>
<td>2.3±0.3</td>
</tr>
</tbody>
</table>

*a Mean±SD of twenty measurements; *Mean±SD of six measurements; *Formulation from Table 1.

Table 4. Constant rate (k) values (in mg•mL⁻¹/min) and r² of zero order kinetic model applied to the different formulations of genistein and daidzein.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Daidzein k values</th>
<th>Daidzein r² coefficient</th>
<th>Genistein k values</th>
<th>Genistein r² coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>CROS</td>
<td>1.487</td>
<td>0.9994</td>
<td>1.672</td>
<td>0.9996</td>
</tr>
<tr>
<td>CROS-SDS</td>
<td>1.699</td>
<td>0.9855</td>
<td>1.944</td>
<td>0.9864</td>
</tr>
<tr>
<td>CROS-POV</td>
<td>1.084</td>
<td>0.9957</td>
<td>0.820</td>
<td>0.9965</td>
</tr>
<tr>
<td>CROS-POV 10</td>
<td>1.301</td>
<td>0.9949</td>
<td>0.699</td>
<td>0.9974</td>
</tr>
<tr>
<td>DC</td>
<td>1.058</td>
<td>0.9997</td>
<td>0.815</td>
<td>0.9892</td>
</tr>
</tbody>
</table>

Figure 2. Genistein (A) and daidzein (B) release from different tablets (CROS-SDS, CROS, CROS-POV, CROS-POV 10 and CD). *p<0.05.
Preparation and characterization of solid oral dosage forms containing soy isoflavones
Stela R. de Oliveira et al.


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