BIOPHARMACEUTICAL AND MARKETING EVALUATION OF DIOSMIN- AND HESPERIDIN-CONTAINING PRODUCTS ON THE BULGARIAN MARKET

Nadezhda Ivanova¹, Yozlem Hyusein², Iliya Slavov³, Ivo Kumanov⁴

¹Department of Pharmaceutical Technologies, Faculty of Pharmacy, Medical University of Varna
²Student, Faculty of Pharmacy, Medical University of Varna
³Department of Biology, Faculty of Pharmacy, Medical University of Varna
⁴Department of Organization and Economics of Pharmacy, Faculty of Pharmacy, Medical University of Varna

ABSTRACT

INTRODUCTION: Diosmin and hesperidin are commonly used flavonoids in the therapy of vascular diseases.

AIM: This study aimed to present an independent evaluation of the market status, quality and biopharmaceutical characteristics of diosmin- and hesperidin-containing oral tablet-products (DHCPs) on the Bulgarian market.

MATERIALS AND METHODS: Seven products, among which medicines (used as reference) and food supplements, with sustainable or growing market were selected for the survey: Detralex 500 mg, Phlebodia 600 mg, Dioket 600 mg, Novarix 650 mg, Asketon 500 mg, Venocode and Dih max 1000 mg. Sales analysis for 2016, 2017 and 2018 (year-to-date) was done with the kind support of Iqvia TM. All products were subjected to European Pharmacopoeia (EP) tests for tablet quality - disintegration, resistance to crushing, uniformity of mass and uniformity of dosage units. Biopharmaceutical profile regarding tablet drug release and dissolution potency was investigated on EP Apparatus 2 (Paddle method).

RESULTS: Although all products were found to almost fully fulfill the EP criteria, extremely unsatisfying drug release was established in all tested media (pH 1.5, pH 4.5 and pH 7.2), reaching not more than 1.6% of the labeled content after 24 hours for the best performing products – Novarix and Venocode.

CONCLUSION: These results were not surprising considering diosmin and hesperidin’s water insolubility and respective low bioavailability. However, it would be reasonable to approach these two bioactive compounds technologically in preformulation stage in order to improve their solubility and therapeutic potency.

Keywords: diosmin, hesperidin, medicines, food supplements, tablets quality, drug release

Address for correspondence:
Nadezhda Ivanova
Faculty of Pharmacy
Medical University of Varna
84 Tzar Osvoboditel Blvd
9002 Varna
e-mail: nadejda__iv@abv.bg

Received: November 27, 2018
Accepted: December 21, 2018
INTRODUCTION

Structure, Sources and Isolation

Diosmin and hesperidin are flavonoids widely used in the treatment of diseases of microcirculatory and vascular origin such as venous insufficiency, varicose veins, hemorrhoids, edemas, post-operative conditions, etc. Both the flavon (Fig. 1A) and the flavanon glycoside (Fig. 1B) possess vasoprotective and venotonic properties (1-14). Diosmin differs from hesperidin by a double bond present in the structure of the former between C₂ and C₃ (Fig. 1) (1-3). Although both glycosides are naturally occurring in the families of Rutaceae, Lamiaceae, Apiaceae, Scrophulariaceae (S. nadosa) (2-10), the industrial sector uses semisynthetic diosmin derived from hesperidin by a suitable oxidation reaction (I₂/pyridine, I₂/dimethylsulfoxide or other) (1-3,11,15-18). Hesperidin is most commonly isolated from dry orange or citrus peels (Citrus sinesis, L., Citrus aurantium, L., Citrus lemon, L., and other Citrus species) (3,8,10).

Characteristics

The substances appear as greyish-yellow or light yellow hygroscopic powders. They are practically insoluble in water and alcohol, soluble in dimethyl sulf oxide and dilute solutions of alkali hydroxides (2,19).

Pharmacokinetics

In vivo diosmin and hesperidin are absorbed through their aglycone forms - diosmetin and hesperetin, respectively, which are products of the intestinal flora-mediated metabolism (1,2,7,9,12,13). However, the latter are not proven to be active metabolites, as they arise due to biotransformation in the gastro-intestinal tract (GIT), but once absorbed, further on undergo glucuronidation and biodegradation to fenolic derivatives, while unmetabolized forms are not found in plasma (7,9,12). For main metabolites are deemed the 3-O-Glucoronide, 7-O-Glucoronides and 3,7-O-Glucoronide conjugates of the aglycoons (2,7,12,13). Generally, diosmin and hesperidin undergo urine excretion (1,2,7,9,12). The biological half-life (t₁/₂) of diosmetin (or more particularly its conjugated forms) is estimated to be 26-43 hours (1). Unabsorbed diosmin and hesperidin are eliminated with the feces (1,2).

Pharmacodynamics

Several mechanisms of action are suggested to be responsible for the beneficial effects of the compounds on the vascular system. First, as flavonoid representatives, they possess a so-called vitamin P-action, manifesting in decrease in vascular permeability and increase in capillary sustainability and elasticity (6,8,11). The aforementioned effects are hypothesized to be due to interference with catecholamine's metabolism. The flavonoids prolong the extraneuronal presence of noradrenaline and its vasoconstrictive action by inhibition of the catechol-O-methyl transferase (COMT-enzyme) and by binding the free plasma ferric and copper ions in inactive chelate complexes (the ions in question are catalyzers of catecholamine's oxidation) (20). Another theory devotes the P-vitamin action to an inhibitory activity on the hyaluronidase family of enzymes, which are responsible for the degradation of hyaluronic acid. This extracellular constituent is essential for vascular health for it is known to strengthen the vascular walls by decreasing their permeability (21). Next, diosmin and hesperidin have an anti-inflammatory effect on the vessels due to prostaglandin E2 (PGE2), thromboxane A2 (TxA2) and leukocyte activation, migration and adhesion inhibitory activity (1,2,4,6,11,14,22). The flavonoids also exhibit antioxidant properties owing to their ability to inhibit the NO-oxide synthase and block free-radical chain reactions. This quality of theirs favors the vessels' lumen condition through an antiatherogenic mechanism (1,2,4,5,9,14,22). Last, both flavonoids have shown angiotensin-converting enzyme (ACE) inhibitory activity, hence they reduce pressure in circulation and this way additionally facilitate the healing of vascular-related diseases and complications (23). Diosmin and hesperidin are proven to possess...
also other effects, unrelated to their vasoactive properties, such as antineoplastic, antiviral and antifungal (1,24,25).

Biopharmaceutical Properties

In order to materialize all these desirable effects in patients though, diosmin and hesperidin need to be bioavailable after oral administration. This is crucial consideration when it comes to these particular drugs. Both compounds belong to class IV of the Biopharmaceutical Classification System (BCS) and thus possess low water solubility and low permeability (2,3,7-9,14,19,26). While the low permeation rate is not so critical since the glycosides (if dissolved!) degrade to easily absorbable aglycons (diosmetin and hesperetin), their water insolubility is a highly limiting factor for pharmaceutical availability, systemic absorption and oral bioavailability. Therefore, the dosage form formulation, including substance processing, adjuvants, type of carrier system, technological operations etc., has major role in achieving optimized therapeutic response. In this regard, the use of diosmin and hesperidin in micronized fraction appears to be indispensable for their potency as pharmaceuticals (3,7-9,14). The smaller-sized particles benefit the solubility rate of slightly soluble and practically insoluble drugs by enlarging their surface area with the dissolvent. However, as mentioned before, many other technological factors are to be considered for high pharmaceutical availability.

AIM

The present study aims to compare the quality and biopharmaceutical properties of diosmin- and hesperidin-containing (or diosmin alone) oral tablet products (DHCPs), at the same time making a parallel with their market shares in Bulgaria for the past 3 years. In the last years, the majority of new competing DHCPs manufacturers register food supplements rather than medicines out of regulatory and convenience considerations. As a result, alternatives to the conventionally adopted combination of 450 mg diosmin+50 mg hesperidin or 600 mg diosmin tablets, being new combinations with other natural vasoprotectors (collagen, hyaluronic acid, escin etc.) or new drug concentrations, multiply relatively fast. At the same time, medicines as Detralex (450 mg diosmin +50 mg hesperidin) and Phlebodia (600 mg diosmin) keep holding the major market share on DHCPs in Bulgaria as a consequence of their affirmed long-standing presence and quality by default (for they are a subject of medicine regulation unlike food supplements). It is a question, even among the medical and pharmaceutical society, whether all these alternatives on the market possess the same quality or somewhat excel the potency of the referent products. In sake of objectivity, it is worth mentioning that the flavonoids in question are primarily subject of medical prescription in Europe, but at the same time provided mostly as food supplements on the US market (12).

Before proceeding to the experimental part exhibition, we would like to emphasize that our assessment was based entirely on in vitro methods and prognoses. It does not concern the potential benefits of additional active ingredients in tablets in vivo (as hyaluronic acid, escin, collagen, etc.) and regards only diosmin/hesperidin content, properties and release behavior as well as tablet quality.

MATERIALS

Hesperidin standard 97% was purchased from Acros Organics Belgium, diosmin:hesperidin 9:1 commercial mixture micronized (DHM9:1) was purchased from Shaanxi Pioneer Biotech Co., Ltd., China, sodium hydroxide, di-sodium hydrogen phosphate, potassium dihydrogen phosphate, sodium chloride were purchased from Thermo Fisher Scientific, 0.22 µm pore size PES syringe filter – from Filters Fioroni, Spain.

METHODS

Marketing Analysis

Sales analysis for all products (2016-2018-year to date (YTD)) was performed with the aid of Iqvia™ data base. The sales in packages and BGN (summarized for all product variations – for example 30 tablets package + 60 tablets package + 90 tablets package) were presented on pie charts.

Analytical Method

Diosmin and hesperidin determination was performed by UV spectrophotometric method on Thermo Scientific Evolution 220 UV/Vis Spectrophotometer. Spectra of DHM9:1 and hesperidin standard were scanned in 0.25 M NaOH solutions. Absorption maxima were found at 267 nm for DHM9:1 and at 283 nm for pure hesperidin (Fig. 2A
Biopharmaceutical and Marketing Evaluation of Diosmin- and Hesperidin-Containing Products on the Bulgarian Market

and B). Standard calibration curves of DHM9:1 and hesperidin were built in 0.25 M NaOH in concentration range of 1-50 mg/L, for each at both wavelengths (WL) in order to establish: 1) whether the presence of hesperidin will affect linearity for diosmin at 267 nm when in mixture 9:1; 2) whether the standard solutions of hesperidin will show reliable linearity in absorbability at 267 nm, even if the absorption maxima of the compound is found at 283 nm; 3) accordingly, whether diosmin and hesperidin can be determined simultaneously in mixture 9:1 at 267 nm via this method, and 4) what would the absorptivity and linearity of diosmin alone at 267 nm be, considering the standard curve of DHM9:1 and hesperidin at the same WL. Detailed information about standard solutions, concentrations and resulting calibration curves is presented in Table 1 and Figure 3.

The aforementioned method was found to be suitable for simultaneous determination of diosmin and hesperidin for it shows good linearity ($R^2>0.997$) and sufficient for the purpose of this study limit of detection (LOD).

![Fig. 2](image1.png) UV spectra of DHM9:1 (A) and hesperidin (B) in 0.25 M NaOH solution at concentration 25 µg/mL

![Fig. 3](image2.png) Standard calibration curves of hesperidin at 267 nm (A), of hesperidin at 283 nm (B), of DHM9:1 at 267 nm (C) and diosmin at 267 nm (D)

Table 1. Standard solutions of DHM91 and hesperidin standard in NaOH 0.25 M

<table>
<thead>
<tr>
<th>Standard solutions of Hesperidin, mg/L</th>
<th>Standard solutions of DHM9:1, mg/L</th>
<th>Concentration of Diosmin in standard solutions of DHM9:1, mg/L</th>
<th>Concentration of Hesperidin in standard solutions of DHM9:1, mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>1.00</td>
<td>0.90</td>
<td>0.10</td>
</tr>
<tr>
<td>1.25</td>
<td>1.25</td>
<td>1.13</td>
<td>0.13</td>
</tr>
<tr>
<td>1.67</td>
<td>1.67</td>
<td>1.50</td>
<td>0.17</td>
</tr>
<tr>
<td>2.50</td>
<td>2.50</td>
<td>2.25</td>
<td>0.25</td>
</tr>
<tr>
<td>5.00</td>
<td>5.00</td>
<td>4.50</td>
<td>0.50</td>
</tr>
<tr>
<td>9.00</td>
<td>10.00</td>
<td>9.00</td>
<td>1.00</td>
</tr>
<tr>
<td>10.00</td>
<td>12.50</td>
<td>11.25</td>
<td>1.25</td>
</tr>
<tr>
<td>11.25</td>
<td>20.00</td>
<td>18.00</td>
<td>2.00</td>
</tr>
<tr>
<td>15.00</td>
<td>25.00</td>
<td>22.50</td>
<td>2.50</td>
</tr>
<tr>
<td>22.50</td>
<td>33.33</td>
<td>30.00</td>
<td>3.33</td>
</tr>
<tr>
<td>25.00</td>
<td>50.00</td>
<td>45.00</td>
<td>5.00</td>
</tr>
<tr>
<td>50.00</td>
<td>100.00</td>
<td>90.00</td>
<td>10.00</td>
</tr>
</tbody>
</table>
EUROPEAN PHARMACOPOEIA TESTS FOR TABLETS

Uniformity of Mass

Twenty tablets of each DHCP were individually weighed on analytical balance. Average mass and standard deviation (SD) were determined.

Uniformity of Dosage Units – Mass Variation Method

According to the EP recommendations, the test for uniformity of dosage units for film-coated tablets (as all tested DHCPs are) was carried out by the mass variation method (19). Ten tablets were weighed and examined for active substance content. Each tablet was pulverized and dispersed in sufficient quantity of 0.25 M NaOH solution. The resulting slurry was transferred to a 50 mL volumetric flask and diluted up to the mark with 0.25 M NaOH. After effective homogenization of the mixture, a sample was withdrawn, filtrated (0.22 µm pore size PES syringe filter), properly diluted and analyzed spectrophotometrically for drug content. Based on the results, acceptance value (AV) was calculated (19).

Resistance to Crushing

Resistance to crushing of tablets was performed on Erweka Tablet Hardness tester (125 series). Ten tablets of each product were subjected to the test. Average hardness was calculated.

Disintegration

Disintegration test for film-coated tablets was performed on EP Apparatus A (Erweka Disintegration tester ZT 220 series). Six tablets of each product were subjected to the test in preliminary heated at 37±2 °C distilled water. Disintegration time was determined as the time needed for all six tablets to disintegrate completely.

In Vitro Dissolution Study

Solubility Study

Prior to the study, test for solubility of DHM9:1 in all selected release media (hydrochloric acid solution (HAS) pH 1,5, phosphate buffer solution (PBS) pH 4,5 and PBS pH 7,2) was carried out. The substance was added in excess to each solution and kept under continuous stirring for 24 hours in a tempered room (25°C). At the end of the study, sample from the supernatant was withdrawn, filtered and analyzed for drug concentration. The measured concentration was perceived as saturation point for DHM9:1 in the given solvent under the above described conditions.

In regard to the substances poor water solubility and related problematics in ensuring „sink” conditions during test, (dissolution test) was performed by two methods – Method I (Standard): on EP Apparatus 2 - Paddle method (Pharma test dissolution tester PT-DT70), and Method II: on flow-through cell resembling setting (Fig. 4). The parameters of the studies are presented in Table 2.

RESULTS AND DISCUSSION

In this section, we present the results using a code name for each product (Product A, B, C etc.), in order to avoid conflict of interests. Where the prod-
Biopharmaceutical and Marketing Evaluation of Diosmin- and Hesperidin-Containing Products on the Bulgarian Market

**Table 2. In vitro drug release tests - parameters of the studies**

<table>
<thead>
<tr>
<th>Method</th>
<th>Type of system</th>
<th>Sink conditions</th>
<th>Time</th>
<th>Release media</th>
<th>Volume, mL</th>
<th>Rotation speed, rpm</th>
<th>Temperature, °C</th>
<th>Flow-in speed</th>
<th>Flow-out speed</th>
<th>Sampling and measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. EP Apparatus 2: Paddle method (Method I)</td>
<td>closed</td>
<td>no</td>
<td>0-1h</td>
<td>HAS pH 1.5</td>
<td>900</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-4h</td>
<td>PBS pH 4.5</td>
<td>900</td>
<td>100</td>
<td>37±0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-24h</td>
<td>PBS pH 7.2</td>
<td>900</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II. Flow-through cell resembling setting (Method II)</td>
<td>opened</td>
<td>yes</td>
<td>0-1h</td>
<td>HAS pH 1.5</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-4h</td>
<td>PBS pH 4.5</td>
<td>50</td>
<td>x</td>
<td>approximately 37 4 mL/min (80 drops per min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-12h</td>
<td>PBS pH 7.2</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Samples from the release media were withdrawn at chosen times (through 5 µm pore size filter) and analyzed spectrophotometrically for diosmin and hesperidin content. Concentration [mg/L] was extrapolated to [mg] drug released in 900 mL and % drug released was presented knowing the labeled drug content in tablets. The buffer solution, collected in the receiving compartment, was analyzed for diosmin and hesperidin content at chosen times. Drug concentration [mg/L] was extrapolated to % drug released, knowing the exact volume of the collected buffer at the time of the measurement and the labeled drug content. |

Product is a medicine, index [m] will be found in the upper right corner of the initials.

**Sales Analysis**

Presented on Figure 5 is the sales analysis of products from A to G for 2016, 2017 and 2018 YTD. As can be seen from the figure, leaders of the market are all medicines, whereas the number and total share of the food supplements grow with each year, but still expectedly, separately they have much fewer sales. Another tendency to be noted is the increase in the total consumption of DHCPs.

**Quality of Tablets**

Results of the tests regarding tablet quality are summarized in Table 3. All tablets were found to comply with the EP criteria for uniformity of mass and to possess substantial hardness above 200 N. Even though there are no referent values in EP for the latter parameter, the hardness of a tablet should provide sustainability, at the same time not affecting negatively its disintegration. Since no producer has declared the product to possess modified release properties, we accepted ≤30 minutes as reference value for disintegration. Tablets of all products were found to disintegrate within 30 minutes, except product B - 73 minutes. This observation we attribute to the lack of superdisintegrants in the composition of Product B, as well as to the excessive hardness of the tablet (>300N). However, knowing the poor water solubility of diosmin and hesperidin, slower disintegration is highly unlikely to play a crucial role in the in vivo performance of the products. Calculation of AV for uniformity of dosage units showed one critical value for Product B and one drastically above the EP criteria value (Product C).
**Fig. 5.** Sales analysis of selected DHCPs for 2016-2018 YTD in packages and BGN

**Table 3.** Quality of tablets

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>UNIFORMITY OF MASS</th>
<th>UNIFORMITY OF DOSAGE UNITS</th>
<th>DISINTEGRATION</th>
<th>RESISTANCE TO CRUSHING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average mass, mg</td>
<td>±SD, %</td>
<td>Average drug content, %&lt;sup&gt;a&lt;/sup&gt;</td>
<td>±SD, %</td>
</tr>
<tr>
<td>Product A&lt;sup&gt;m&lt;/sup&gt;</td>
<td>688</td>
<td>0.65</td>
<td>108.32</td>
<td>3.65</td>
</tr>
<tr>
<td>Product B</td>
<td>848</td>
<td>0.53</td>
<td>103.20</td>
<td>7.76</td>
</tr>
<tr>
<td>Product C</td>
<td>634</td>
<td>2.39</td>
<td>99.05</td>
<td>12.16</td>
</tr>
<tr>
<td>Product D</td>
<td>976</td>
<td>0.56</td>
<td>≤5.00</td>
<td>109.01</td>
</tr>
<tr>
<td>Product E&lt;sup&gt;m&lt;/sup&gt;</td>
<td>944</td>
<td>0.58</td>
<td>124.22</td>
<td>8.29</td>
</tr>
<tr>
<td>Product F&lt;sup&gt;m&lt;/sup&gt;</td>
<td>730</td>
<td>1.37</td>
<td>109.99</td>
<td>8.88</td>
</tr>
<tr>
<td>Product G</td>
<td>1278</td>
<td>0.65</td>
<td>109.15</td>
<td>5.79</td>
</tr>
</tbody>
</table>

<sup>a</sup>SD - standard deviation
<sup>b</sup>Drug content found in tablets, expressed as percent (%) of the labeled content
<sup>c</sup>AV was calculated according to the EP recommendations – chapter 2.9.40 Uniformity of dosage units, Mass variation
<sup>d</sup>The value of hardness [N] has excelled the apparatus limitations of detection (10-300 N), SD could not be calculated
Solubility

In diosmin and hesperidin micronized powder 9:1 were found: saturate HAS pH 1.5 at 897 µg/L, PBS pH 4.5 at 1462 µg/L and PBS pH 7.2 at 2125 µg/L. According to the results obtained and the EP classification, DHM9:1 qualify as very slightly soluble in HAS pH 1.5 and slightly soluble in PBS pH 4.5 and pH 7.2.

Drug release profiles of tested DHCPs, obtained by Method I are presented on Fig. 6A. Very unsatisfying prognosis for pharmaceutical availability for all products was established, as the highest percent drug released reached no more than 1.6% of the labeled content (Product B and C). Fig. 6B on the other hand, demonstrates the significance of “sink” conditions for the drug release, by presenting the release profile of a randomly selected product (Product B) obtained by the two described methods - Method I (standard method, but „sink” requirements are not met according to the drug solubility test) and Method II („sink” conditions are ensured). Comparison of both dissolution profiles of Product B showed differences in the rate constant of the dissolution process, but no substantial difference in the cumulated drug released after 12 h; hence, the unsatisfying drug release of diosmin and hesperidin from the tablets cannot be attributed to the lack of „sink” conditioning in the classical closed dissolution tester system.

The results obtained in this study we perceive as informative in sake of comparison between the selected products. However, further in vivo studies of DHCPs and validation of analytical methods for determination of diosmin and hesperidin are needed to understand whether the extremely low pharmaceutical availability corresponds to just as low level of envisaged bioavailability. Authors researching this area seem to be unanimous about the challenging evaluation of diosmetin plasma concentrations due to the necessity of preliminary degradation of conjugated forms and precise definition of the latter. Therefore, the available pharmacokinetic data for diosmin is inconsistent and highly variable (7, 9, 12). As the improvement of diosmin and hesperidin analysis is not a primary topic of our study, we rely on several recent pharmacokinetic reports to cross-check the credibility of our findings. For example, Russo et al. (2018) compare the pharmacokinetic profile of diosmin following oral administration of a 500 mg single dose µSmin® (a diosmin flavonoid complex) (test) and unformulated micronized diosmin (reference). The maximum plasma concentrations (Cmax) detected by the authors are 50.3±22.6 ng/mL and 2.4±1.9 ng/mL, respectively (7). Assuming the average plasma volume of an adult patient to be 2.75 L, these plasma levels represent 0.06% and 0.003% of the initial dose administered (500 mg diosmin correspond to 246.8 mg aglycone diosmetin). Another study, performed by Silvestro et al. (2013), shows Cmax of diosmetin following oral intake of 450 mg diosmin to be 6049.3±5548.6 pg/mL (12). Under the same assumptions, this Cmax represents 0.0075% of the initial dose administered (450 mg diosmin correspond to 222 mg diosmetin). In comparison, the predicted values for pharmaceutical availability in our study vary between 0.33-1.57% among the products. Certainly, low pharmaceutical availability is a key factor for low plasma concentration and low oral bioavailability.

CONCLUSION

The main problem with DHCPs appears to be the very low water solubility of the substances even in micronized fraction, leading to unsatisfying pharmaceutical availability (<1.6%). The need exist of additional technological approaches to improve diosmin and hesperidin’s in vitro and in vivo performance. Such achievement could potentially benefit the patients’ therapy and reduce side effects, originating from the high dose of unabsorbed flavonoids (often manifesting as gastro-intestinal disorders). Furthermore, it would definitely have a positive economic impact. We hope to be able to present a successful step in this direction in a future report.
REFERENCES


