Gastro-resistant Pellets of Didanosine obtained by Extrusion and Spheronization: Assessing the Production Process

Newton ANDRÉO-FILHO *1,2, Leticia PESSOLE 1, Michele G. ISSA 1, Cláudio VILLELA 1 & Humberto G. FERRAZ 1

1 Department of Pharmacy, Laboratory of Pharmaceutics, College of Pharmaceutical Sciences, University of São Paulo, Avenida Prof. Lineu Prestes, 580 Bloco 13, Butatã, CEP: 05508-900, São Paulo – SP, Brasil
2 Course of Pharmacy, University of Sorocaba, Rodovia Raposo Tavares, km 92.5, Trevo, CEP: 18023-000 – Sorocaba, Brasil

SUMMARY. The aim this work was develop gastro-resistant pellets of didanosine as well as study the impact on the pellets properties, regarding the way as the binder was added and drying process used. The pellets formation was accompanied by analysis of morphological parameters and didanosine dissolution. In the most cases, pellets showed diameter around 1.0 mm and shape parameters acceptable. The variations of the process did not interfere significantly in pellets size. In turn, drying in fluid bed favored the dissolution of didanosine, in contrast to binder addition on powder form that impaired. In another hand, this last resulted in the best aspect factor (about 1.1). Gastro-resistant pellets showed adequate dissolution, compatible with this type of dosage form. The variables of process studied enabled obtain pellets with characteristics of shape and dissolution just slightly different, indicating flexibility of the formulation for production of gastro-resistant pellets of didanosine.

INTRODUCTION

Pellets are spherical granules 0.5 - 1.5 mm in diameter produced by the agglomeration of fine powder with a liquid binder in a mixer, pan coating or spray drying machines; can also be produced by hot-melt extrusion. As a drug release system, they offer some technological advantages such as better flow, less friable dosage form, narrow particle size distribution and ease of coating with polymeric film 1-3.

Among the methods used to obtain pellets, extrusion and spheronization is the most widely described 4. This process involves four steps: 1) Granulation–preparation of moist mass; 2) Extrusion–moulding the moist mass into cylindrical bars by compressing it against a perforated net; 3) Spheronization–breaking down the cylindrical extrudates, and then moulding them into spherical particles; 4) Drying–elimination of solvent or liquid binder in an oven or fluid bed 4,5. The drying step is particularly relevant since some quality parameters, like porosity, depend on the type of drying process employed 4,5.

To obtain pellets by extrusion/spheronization, inert excipients must be added to the formulation so as to facilitate the compacting process, and also to provide the moist mass with plasticity 4. In that sense, the cellulose derivatives are excipients of great importance, microcrystalline cellulose being the first choice excipient for the production of pellets 7,8.

Apart from the technological advantages, pellets also have therapeutic ones. As a multi-particle pharmaceutical dosage form, pellets spread up uniformly throughout by gastrointestinal tract, avoiding high local concentration of drug, thereby reducing the risk of toxicity observed in tablets, which have a more localized presence in some areas of the gastro-intestinal tract 9-11. This fact can enhance the bioavailability, which potentially may lead to reduction of drug dosage and consequently of its side-effects.

In addition, drug degradation or gastric irritation caused by small release of drug loading in conventional gastro-resistant dosage forms can be reduced by using coated pellets with gastro-re-
sistant polymeric film. This happens because pellets have a smaller time of gastric residence than gastro-resistant tablets.

The above property can be of great interest in the production of medicines loading drugs such as didanosine (ddI), a reverse transcriptase inhibitor antiretroviral of the nucleoside class, which is unstable in acid medium. This drug, initially available as buffered tablets, and others buffered dosage forms, presents great bioavailability variation due to its decomposition in acid medium that is not always prevented by buffering agents. As an alternative to buffering systems, some authors have tried to develop systems able to avoid the contact between didanosine and the stomach acid medium, the gastro-resistant pellets or tablets being exploited the most.

The aim of this work was to develop ddI gastro-resistant pellet formulations, as well as to study the impact of the way of binder addition and drying process on the formulations. The pellet spheroidization process was also assessed based on the alterations of their morphological parameters.

MATERIAL AND METHODS

Pellets production

Pellets with ddI (FUNED, lote 20020727, Belo Horizonte, Brazil) were produced by extrusion/spheroidization method using Caleva Extruder® 20 and Caleva Speronizer® 250 (Caleva Process Solutions, Blandford, England). The procedure consisted in mixing equivalent masses of microcrystalline cellulose PH101 (MCC - Blanver, Cotia, Brazil) and lactose M200 (Henrifarma, São Paulo, Brazil) with ddI. A 10% (w/V) dispersion of polyvinylpyrrolidone (PVP-K30 – ISP, São Paulo, Brazil) in purified water was used as binder liquid. Table 1 shows the tested formulations.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>PEL-I (%)</th>
<th>PEL-II (%)</th>
<th>PEL-III (%)</th>
<th>PEL-IV (%)</th>
<th>PEL-V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddI</td>
<td>19.2</td>
<td>19.4</td>
<td>19.2</td>
<td>9.2</td>
<td>38.8</td>
</tr>
<tr>
<td>MCC PH101</td>
<td>38.3</td>
<td>38.8</td>
<td>38.5</td>
<td>33.9</td>
<td>29.1</td>
</tr>
<tr>
<td>Lactose M200</td>
<td>38.3</td>
<td>38.8</td>
<td>38.5</td>
<td>33.9</td>
<td>29.1</td>
</tr>
<tr>
<td>PVP-K30</td>
<td>4.2</td>
<td>3.0</td>
<td>3.8</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 1. Percent composition of the ddI pellet formulations produced by extrusion and spheroidization.

Granulometric distribution

The pellets obtained were analysed with regard to granulometric distribution using 4 sieves of different mesh openings apart from the base (2.00, 1.19, 0.59, and 0.42 mm). The sieves were previously weighted and the dry pellets were transferred and stirred until all the material was transferred. After, each sieve and its content were weighted. It was used only four sieves in order to restrict the number of groups formed, since the range of particle size between 0.59 and 1.19 mm was considered of interest to carry out the other experiments.

Pellet morphological analysis

The obtained pellets were analyzed with regard to morphology using images obtained with a stereoscope Olympus SD30 and registered with a digital camera Sony DCR-HC15. Then, they were analyzed with the help of software Image Pro-Plus® version 4.5.0.29 to calculate the parameters for aspect, sphericity, mean diameter and Ferret diameter. While the first two parameters refer to the spherical form of the particles, the latter two refer to pellet size. In order to calibrate the images, a standard plate with a 1.00 cm of straight line segment with one hundred divisions was used and its image registered of the same way.

DdI quantification

Standard curve of ddI

The ddI amount in the pellet formulations was determined by spectrophotometry UV-vis (Beckman Coulter DU-600) at 249 nm through...
the standard curve of the ddl between 2 and 24 µg/ml. The absorbance index was registered and the mean, standard deviation and relative standard deviation (RSD) calculated. All analyses were done in triplicate.

Dissolution profile

The dissolution profiles of ddl contained in the pellet formulations (PEL-I a V) were obtained using dissolution equipment Logan D800 (Logan Instruments Corp, New Jersey, USA). 900 ml of distilled and degassed water were used as a dissolution medium. The procedures were carried out at 37 ± 0.5 °C using the apparatus I (basket) described in the United States Pharmacopeia 30th 18. Ten milliliters of the dissolution medium were collected at time of 3, 5, 10, 15, 20, 30, 40 and 60 min. Each sample taken was replaced by an equivalent dissolution medium of same volume. The samples collected were diluted, if necessary, and then analysed by spectrophotometry at 249 nm and the percentage of drug dissolved was determined.

Departing from the pellet formulation dissolution profiles, the values of the dissolution efficiency (DE%) were calculated for each of the repetitions using the trapeze addition method 19, considering time intervals between 0 and 60 min. The results were submitted to statistical analysis using the ANOVA test. The means were compared using the Tukey test, with the significance level being set at 5%.

Variations of the processing conditions to obtain pellets

To verify whether the alterations in the process of obtaining pellets would interfere in the physical characteristics and dissolution profile, four batches of pellets were produced departing from the PEL-III formulation.

To do this trial, two batches of 50 g formulation PEL–III were produced. The difference between the two was the way in which the binder agent was added. For the PEL-III-A, binder PVP-K30 was added in aqueous dispersion at 20% (w/V) until an adequate concentration was reached. Distilled water was added to complete the wetting of the mass. For the PEL-III-B, on the other hand, the exact amount of binder powder prescribed in the formulation was added. Purified water was also added to complete the wetting of the mass.

The batches were extrudated as described earlier. For spheronization, a period of 10 min was adopted for the accomplishment of the process. The process was interrupted every 2 min to collect a sample of about 1 g each. The samples collected were dried in a tray-drying oven for 2 h, after which they were submitted to morphological analysis. This procedure was adopted to follow the kinetics of transformation of extruded into pellets.

At the end of the spheronization process, the batches were halved and submitted to a different drying process. One half of each batch was dried in a tray-drying oven (PEL-III-A-O and PEL-III-B-O) with forced air circulation for 2 h at 45 °C, whereas the other was dried in fluid bed Hüttlin Mycrolab® (Hüttlin GmbH, Steinen, Alemanha) (PEL-III-A-F and PEL-III-B-F) for 30 min under constant air flow for approximately 20 m3/h at 45 °C.

The pellets obtained were analyzed with regard to granulometric distribution, morphology, amount of ddl and dissolution profile as previously described.

Pellet coating in fluid bed

Coating material

Kollicoat MAE 100P® (BASF, São Paulo, Brazil), an association of metacrylic/etilacrylic acid (1:1), and two tensioactive agents, sodium laureyl sulphate and polyssorbate 80, were used as gastro-resistant coating material for the pellets.

The polymeric suspension was prepared through the dispersion of 13.5 g Kollicoat MAE 100P® in purified water under agitation. The dispersion was kept under constant stirring for one hour, and then, propilenoglycol (1.34 g) was added. After 30 min, the opacifying suspension previously obtained through the dispersion of 0.90 g titanium dioxide and 3.60 g talc powder in purified water and Kolidon 30® (0.46 g) (BASF, São Paulo, Brazil) was added. The preparation was kept under constant stirring for more 30 min.

Pellet coating

Pellets PEL-III-A-F were prepared as described earlier, and then submitted to coating process in fluid bed. To that matter, about 40 g of pellets were placed in a fluid bed chamber and fluidized through air flow 11 m3/h at 60 °C. The coating material was applied at a rate of 1.375 g/min under 0.45 bar of pressure for 30 min (PEL-III-A-F-20) or 40 min (PEL-III-A-F-25) for a theoretical weight gain of approximately 20% and 25%, respectively.
Dissolution trials of gastro-resistant pellets

The assessment of the gastro-resistant formulations produced (PEL-III-A-F-20 and PEL-III-A-F-25) was carried out as described by Andréo-Filho et al. 15. To that matter, 750 ml of the hydrochloric acid 0.01 M solution in water were transferred to the dissolution containers and kept at 37 ± 0.5 °C under rotation (75 rpm) in apparatus I. Ten milliliter of the dissolution medium were collected at time intervals of 10, 20, 40, 60, 80, 100 and 120 min. Once the last sample was collected, 250 ml of phosphate buffer 0.05 M (pH 6.8) were added to the dissolution containers. The pH was adjusted to 6.8 using NaOH solution. Samples were then collected at time intervals of 130, 140, 160 and 180 min, diluted if necessary, and then analysed by spectrophotometry at 249 nm to determined the percentage of ddI dissolved.

RESULTS AND DISCUSSION

The process to obtain pellets by extrusion and spheronization was able to produce spherical pellets with surfaces smooth, apparently. The majority of variations regarding both process and formulation had little or no impact on the final diameter of pellets. This can be verified by granulometric distribution and morphological analysis.

In the first assay, more than 70% of pellets mass showed diameter between 0.59 and 1.19 mm (Fig. 1a) regardless of the ddI proportion (20, 30 and 40%) and amount of binder agent (3.0, 3.8, or 4.2%).

Likewise, the morphological analysis using the captured images by digital camera coupled to stereoscope (Fig. 2) show that the mean diameter ranged between 0.943 ± 0.206 (PEL-III) and 1.171 ± 0.149 (PEL-IV), except for PEL-V, whose mean diameter was 1.378 ± 0.175 (Table 2).

In fact, the mean diameters close to 1 mm was expected, once the diameters of holes on the extruder screen had this size. According to Gandhi et al. 2, the size of the holes of the screen is the determining factor on pellet diameter. The exception observed for PEL-V can be attributed to the lower proportion of MCC in the formulation, which generated a wet mass with lower plasticity and small ability to retain the binder liquid. In fact, MCC has ideal physical properties, including ability to retain and distribute the water used for wetting the powder mixture, which are essential to the extrusion process and moulding during the spheronization 2,3. Therefore, the lower concentration of MCC may have favored the formation of small particles no-molded, which during spheronization process were incorporated on the bigger ones, resulting in an enhanced in mean diameter of the particles.

The morphological analysis of the formulations also revealed that the shapes of the particles were spherical, which can be verified by the aspect and sphericity measure (Table 2). Moreover, the augmented images (Figure 2B, D and F) indicate that the surface of pellets is smooth.

Shape parameters, aspect and sphericity, shown up adequate. According to Sanches-Lafuente et al. 16, the aspect parameter relates up with the greatest and smallest axis of the particle in analysis. To this parameter perfectly spherical particles must have value equal to one. Already the sphericity relates the perimeter to the second with the area of the polygon multiplied by 4π, and the expected values shall be near to one too. In a study to evaluate a standardised procedure to assess the shape of pellets through image analysis Podczeck et al. 20 suggest to be adopted the value of 1.1 as the upper limit possible for aspect parameter. Chopra et al. 21, in turn, consider the value 1.2
as the upper limit. If considered the last value, only PEL-I formulation showed be adequate regarding this parameter (aspect = 1.179 ± 0.106). However, for the sphericity parameter all formulations analyzed showed adequate with values close to one and relative standard deviation below to 6% in the most cases.

The ddl quantification using spectrophotometry shown adequate with \( r^2 = 0.9996 \) and RSD below 2%, except to 2 µg/mL (RSD = 6.5). The dissolution of ddl loaded in pellets (PEL I to V) was considered adequate since it has released more than 80% of the drug in less than 10 min for all formulations (Fig. 3a). This releasing index is in accordance with the desired objective, according to which ddl must be released at a short period of time. This is in tandem with the observations of Andréo-Filho et al. 22 that compared the dissolution profiles of different samples of ddl chewable tablet, it was found that about 70% of ddl have been released at time below to 10 min. In fact, it is desirable that ddl release should be quick and intense as shown by Damle et al. 17 on clinical trials for buffered formulations. In that study, the authors determined a period of 36 min to reach for maximum plasmatic concentration (C\(_{\text{max}}\)) after a single dose, suggesting a rapid dissolution of ddl in gastrointestinal tract.

For all formulations tested the DE% indexes indicated the high velocity and amplitude in which ddl was released (Figure 3a and Table 2). This may be attributed to good solubility of ddl in water and the high proportion of lactose in

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Mean diameter (mm)</th>
<th>Feret diameter (mm)</th>
<th>Aspect</th>
<th>Sphericity</th>
<th>DE% a</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEL-I</td>
<td>1.069±0.159</td>
<td>1.116±0.165</td>
<td>1.179±0.106</td>
<td>1.102±0.063</td>
<td>87.00b</td>
</tr>
<tr>
<td>PEL-II</td>
<td>1.108±0.123</td>
<td>1.165±0.143</td>
<td>1.212±0.141</td>
<td>1.070±0.028</td>
<td>87.52b</td>
</tr>
<tr>
<td>PEL-III</td>
<td>0.943±0.206</td>
<td>0.983±0.217</td>
<td>1.260±0.363</td>
<td>1.095±0.104</td>
<td>91.65ab</td>
</tr>
<tr>
<td>PEL-IV</td>
<td>1.171±0.149</td>
<td>1.228±0.164</td>
<td>1.286±0.163</td>
<td>1.107±0.063</td>
<td>91.80ab</td>
</tr>
<tr>
<td>PEL-V</td>
<td>1.378±0.175</td>
<td>1.434±0.204</td>
<td>1.202±0.172</td>
<td>1.084±0.049</td>
<td>95.98a</td>
</tr>
</tbody>
</table>

Table 2. Morphological and dissolution analysis of PEL formulations (I to V). a DE% (n = 3, RSD = 2.15, F = 10.542**): values followed by the same letters do not differ among themselves according to Tukey test (5%). ** significant at 1% probability level.
the formulations. According to Sousa et al., pellets with high amount of water-soluble diluents have their drug more easily released, and this is facilitated even more when the drug itself is also water soluble.

The variance analysis for DE% values revealed that there was a significant difference between formulations (Table 2) and the mean comparison test showed that such difference concerns mainly PEL-I and PEL-II formulations. PEL-III, PEL-IV and PEL-V formulations, on the other hand, did not present significant changes regarding DE%. However, it is important to point out that PEL-IV and PEL-V formulations suffered partial disintegration during the dissolution trial. This became evident with the deposition of particles at the bottom of the dissolution container. Once again, this fact may be attributed to the smaller proportion of MCC in the PEL-IV and PEL-V (about 30%), which hinders the formation of the matrix that provides support for pellet formation. Such finding together with the absence of a statistical significant difference between the DE% of formulations PEL-III, IV and V, led to the selection of formulation PEL-III to be used for assess the impact, regarding morphology and dissolution parameters, of some process changes such as the way in which the binder agent was added (aqueous dispersion or powder), and of the drying process (tray drying oven or fluid bed) on the production process.

Granulometric analysis of the derivations of PEL-III formulation indicated that all of them had more than 80% of the particles ranging from 0.59 to 1.19 mm. A slightly narrower range was observed when the binder agent was added in the form of aqueous dispersion (PEL-III-A-O and PEL-III-A-F), as is shown in Fig. 1b.

The derivations performed with test formulation PEL-III did not present data in which pellet size and shape were any different from the tests previously done. However, the results of mean diameter are in disagreement with the findings by Bashaiwoldu et al. where pellets with lower size were obtained when drying process was carried out in tray-drying oven. In turn, studies of Kleinebudde et al. indicate that both drying processes produce the same phenomenon of shrinkage, suggesting that final size of these pellets are so close. In our results, the size of the pellets dried on fluid bed was slightly lower than on tray-drying oven. This result is in accordance with that obtained by Peres, Rabiskova. In fact, on the second process, since the formulations contain hydrosoluble materials, migration of them together with the water to pellets surface followed by slow solvent evaporation could block the pores. This obstruction could lead an increase of the pressure inside of pellets promoting expansion of them.

On the other hand, values of aspect and sphericity, seem have suffered greater interference of the way the binder agent was added that of drying process. The aspect values to the formulations for which PVP-K30 was used as powder (PEL-III-B-F and PEL-III-B-O) presented values close to one indicating spherical shape, while for binder used as aqueous dispersion the aspect values were greater. The same correlation can not be made with regard to parameter sphericity since all of them showed values close to one.

The assessment of the spheronization process (Fig. 4) using images of pellets samples collected at 2, 4, 6, 8 and 10 min during spheronization, and analyzed in stereoscope, revealed that, initially, the shape parameters tend to improve, approaching one. However, as the process continues, such parameters start to move away from one, which indicates loss of the ideal spherical shape. A similar fact occurred with mean diameter of pellets during
spherization. After an initial reduction, the size of the pellets started to increase.

It is important to highlight that, considering the two different ways in which the binder agent was added, the changes occurred at 6 and 8 min for formulations PEL-III-A and B, respectively, for both parameters. Such fact indicates that the extrudates are quickly broken down into small fragments which are then moulded in the shape of little spheres. Subsequently, the process continues until the particles reach their sphericity maximum with smaller diameter. From that point onwards, the spherical particles formed start to incorporate into their surfaces small fragments of extrudate which are too small to be spheronized in isolation. This increases the diameter of pellets, and that makes them move away from their initial spherical shape. The result confirms the hypothesis earlier presented, where the greater size of PEL-V can be attributed to attachment of particles lower.

Thus, the results suggest that it is possible to determine an optimum time for the spheronization of extrudates. However, this optimum time can vary depending on the formulation composition, as well as on the characteristics of the production process. With regard to the formulations studied, a two-minute difference was observed.

The dissolution trials revealed that all derivations of the PEL-III formulation had more than 80% of their drug released within 15 min (Fig. 3b). Such results confirm those previously discussed, demonstrating that ddl release is very quickly and intense for all formulations and process variations tested. This data confirm that for these pellets formations the ddl solubility (27.3 mg/ml at pH 6.0) governs the dissolution events.

It was verified that addition of powdered binder agent (PEL-III-B-F and PEL-III-B-O) delayed the ddl dissolution of the pellets. This fact was confirmed by the variance analysis, which indicated a significant difference among the DE% values (Table 3), and also by the means comparison test, which indicated significant differences between formulations whose binder agent was added in dispersion and those whose agent was added in powder.

The drying process, in turn, did not produce statistically significant changes in the formulations. However, it is important to point out that the greatest value for DE% was obtained for the formulation that was dried in fluid bed (PEL-III-A-F). This outcome was expected, and is in tandem with Bashaiwoldu et al. who observed that the drying process in fluid bed enables the production of more porous pellets that, consequently, have a greater superficial area, which facilitates drug release. Tray-drying oven, on the other hand, allows humidity to be eliminated more slowly, and that leads to the production of less porous, denser pellets, which may hinder drug dissolution.

There are several reasons why solid formulations should be coated with gastro-resistant films. The main reason is that some drugs, such as ddl, are unstable when in contact with gastric medium, which may lead to drug decomposition and, consequently, loss of pharmacological activity. In acidic solutions (pH lower than 3.0 at 37 °C), about 10% of ddl decomposes leading to the formation of hypoxanthine.

Among the polymers used to confer gastro-resistance to the solid formulations, the derivatives of the metacrylic acid are quite useful due to their insolvency in low-pH mediums. According to the United States Pharmacopoeia 30th, gastro-resistant formulations characterize themselves for releasing at the most 10% of their drug in simulated gastric juice within 2 h. They
also release the drug content in phosphate buffer (pH 6.8) within 45 min at the most.

The results of dissolution tests of coating formulations (PEL-III-A-F-20 and 25), indicate that less than 3% of the ddI content was detected in simulated gastric fluid dissolution medium for both formulations, no existing significant difference between them due to amount of coating material on the pellets (Fig. 5).

The pellet coating process employed seems to have been adequate for two reasons: the releasing characteristic was adequate, and also pellet aggregation during the process was not observed. However, in spite of the process efficiency, deposition of coating material on the inner walls of the fluid bed equipment was verified. This might be related to a weight gain below expected (14.4% for PEL-III-A-F-20 and 19.8% for PEL-III-A-F-25).

**CONCLUSION**

It was possible to obtain gastro-resistant formulations of didanosine pellets. All formulations tested presented adequate morphological characteristics and dissolution, which resulted in spherical particles with good granulometric distribution. Drug release was quick and complete in pH 6.8. The formulation and process variables showed small differences with regard to morphological and dissolution parameters. This may prove useful to the development of pellet formulations. Moreover, by assessing the spheronization process, we could verify the existence of an optimum time for the execution of this step, which enabled the process to produce small-sized and spherical particles.

**Acknowledgements.** The authors thank FINEP (Financiadora de Estudos e Projetos) for financially supporting this work.

---

**Analysed parameters**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Mean diameter (mm)</th>
<th>Feret diameter (mm)</th>
<th>Aspect</th>
<th>Sphericity</th>
<th>DE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEL-III-A-F</td>
<td>0.935 ± 0.129</td>
<td>0.965 ± 0.133</td>
<td>1.147 ± 0.057</td>
<td>1.049 ± 0.041</td>
<td>91.33 a</td>
</tr>
<tr>
<td>PEL-III-A-O</td>
<td>0.953 ± 0.185</td>
<td>0.991 ± 0.206</td>
<td>1.211 ± 0.269</td>
<td>1.093 ± 0.162</td>
<td>87.33 ab</td>
</tr>
<tr>
<td>PEL-III-B-F</td>
<td>0.921 ± 0.116</td>
<td>0.958 ± 0.116</td>
<td>1.101 ± 0.063</td>
<td>1.075 ± 0.063</td>
<td>83.67 b</td>
</tr>
<tr>
<td>PEL-III-B-O</td>
<td>1.036 ± 0.114</td>
<td>1.078 ± 0.118</td>
<td>1.084 ± 0.056</td>
<td>1.072 ± 0.077</td>
<td>84.00 b</td>
</tr>
</tbody>
</table>

Table 3. Morphological and dissolution analysis of derivations of PEL-III formulation. a DE% (n = 3, RSD = 2.24, F = 10.215**: values followed by the same letters do not differ among themselves according to Tukey test (5%). ** significant at 1% probability level.

**REFERENCES**