Multi-layer Tablets: Study of the Critical Parameters by a Compression Simulator
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Purpose
Multi-layer tablets (MLT) are designed for the manufacturing of fixed-dose combination products that simplify the medication regimen and potentially increase the patient’s compliance. MLT are heterogeneous systems in which two layers of compacted powders are separated between them by a discrete interface. The hardness and the delamination tendency of MLT depend not only on the layer composition but also on the deformation property of each layer during tableting. Aim of this work was the study of the influence of layer composition and compaction parameters on the delamination propensity of three-layer tablets for the immediate release of two drugs in combination. The first and third layers were made of sucralfate, a gastric mucosa protector, while the middle layer consisted of ibuprofen lysine, an anti-inflammatory drug

Methods
For sucralfate layer (dose 150 mg), sucralfate gel was granulated with microcrystalline cellulose (SUCR_1) or a mixture of lactose and microcrystalline cellulose (SUCR_2) and dried in Mini Glatt until the residual water was about 15%. Magnesium stearate was added to granulate and mixed in Turbula® for 5 min.

About Ibuprofen lysine layer (dose 342 mg), ibuprofen lysine was granulated with sodium bicarbonate and lactose using an alcoholic solution of polyvinylpyrrolidone (5% w/v) and dried for 2 h in oven at 40°C. Colloidal silica and croscarmellose sodium were added to granulate and mixed in Turbula® for 15 min. Then, magnesium stearate was added to the blend and mixed for 5 additional minutes. The three-layer tablets were manufactured using a Styl’One Evolution Rotary Tablet Press Simulator (Medelpharm, France). The tablets were produced using oblong EURO D punches (17.50 x 8.50 mm), at different pre-compression force (0, 1, 2 and 4 kN) and compression forces (10, 20, 30 and 40 kN). The compaction process was performed using Advanced Analysis Software.

Results
First of all, two types of bi-layer oblong tablets, differing on sucralfate layer composition, were manufactured. In the case of bi-layer SUCR_1, as the pre-compression and compression forces applied increased the bi-layer tablets delaminated during the ejection from the press die. This behaviour was due to the presence of microcrystalline cellulose in the sucralfate layer. The surface roughness of microcrystalline cellulose, which behaves as plastic material, was reduced in the first layer as the pre-compression force increased, decreasing the mechanical interlocking between the two adjacent layers. In the case of bi-layer tablet SUCR_2, in which both lactose and microcrystalline cellulose were present in the sucralfate granulation, no delamination was observed, independently from the pre-compression and compression forces applied. Lactose, which behaves as brittle material, was introduced in the granulation in order to increase the interfacial strength. In fact lactose, which tends to fracture creating new surfaces, helps the adhesion of the layers. Moreover, being lactose fracturing compared to plastic material, it retained more surface roughness for mechanical interlocking of adjacent layers. However, this leads to an increase of the energy of ejection of the bi-layer tablets at compression force of 30 and 40 kN, as the fragmentation of lactose generated an higher surfaces area free from lubricant increasing the friction coefficient.

The three-layers tablets were then manufactured using SUCR_2 formulation for the two layers of sucralfate. As already observed for the corresponding bi-layers tablets, no layer separation was observed, independently from the pre-compression and compression forces applied.

Conclusion
The addition of lactose to the formulation of sucralfate was beneficial for the layer adhesion during the manufacturing of the multilayer tablets. However, the fracture of the brittle material in smallest particles caused an increase of the radial frictions between the tablet and the die wall. Consequently, the ejection energy of the multi-layer tablets increases, especially at higher values of compression forces.