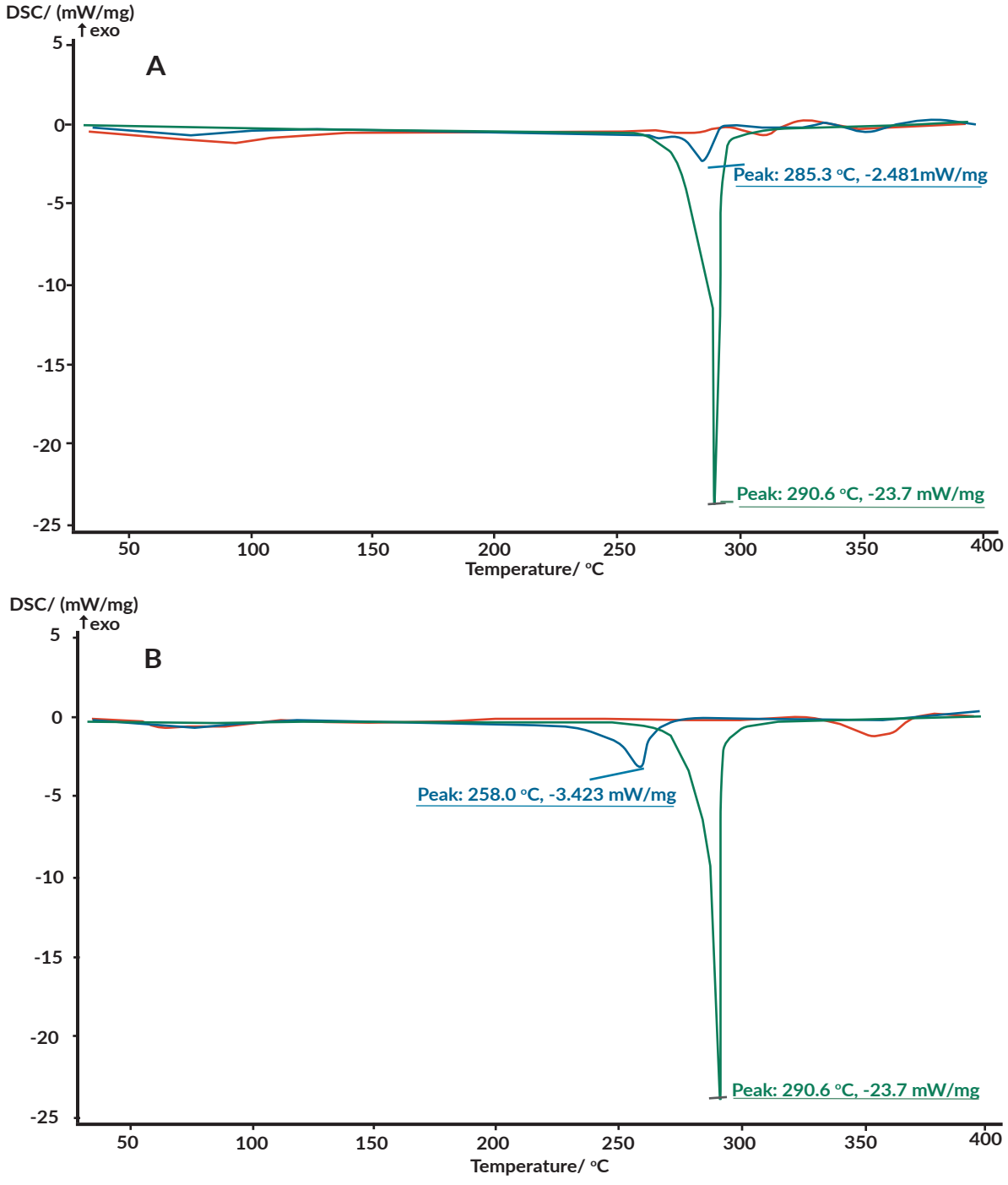

FIGURE 1. DSC analysis of mesalazine and excipients (A - Starch; B - Magnesium stearate; Mesalazine – green; Excipient – red and Mesalazine:Excipient 1:1 - blue)

TABLE 1. The composition of granule – laboratory batches

	Quality (mg/tablet)			
Raw material	LM01	LM02	LM03	LM04
Mesalazine	500	500	500	500
Starch	25.00	37.5	50	66
Purified water*	475	462.5	450	484
Granule (total)	525	537,5	550	566

*Not found in finished intermediate product (granule)

quantity, API: binder ratio 10:1. The third batch employed the ratio 10:0.75 and the last one 10:1.2 (Table 1). A granulometric comparison of the batches (Figure 2) shows that the fourth formulation generates the highest amount (69.1%) of granules in the range of 1000 – 300 µm.

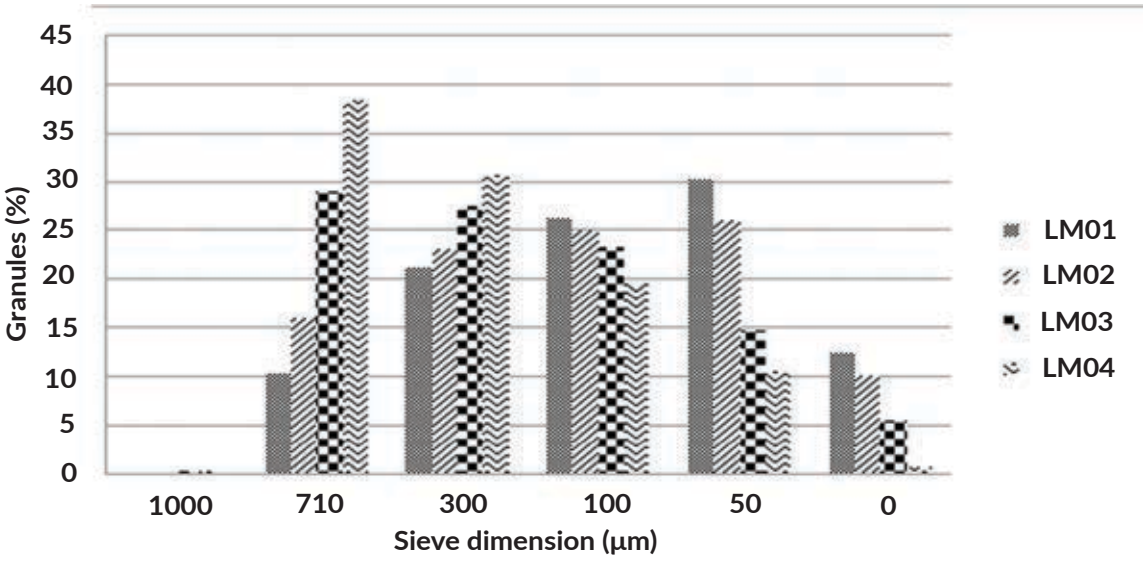

FIGURE 2. The granulometric distribution of mesalazine granules – laboratory batches

Each of the granule batches were mixed with similar amounts of cellulose, and identical amounts of croscarmellose sodium, colloidal silica, talc, and magnesium stearate, in order to obtain 800.00 mg cores. Batches LM01 to LM03 had low apparent powder density and uneven average mass. Batch LM04 showed steadier characteristics. However, the tablet hardness was low, an inconvenient for the coating process. The augmentation of the compression force did not improve the results. A change in the formulation was needed in order to optimize the tableting process.

Laboratory batch LM05 was developed. The granulation formula of LM04 was employed and the diluent was modified. Small amounts of calcium carbonate significantly improve powder compressibility [13]. Calcium carbonate was added to the mixture, representing 4% of the core weight, and the cellulose amount was diminished accordingly. This formula had better results than the previous. Due to the trend of the results, a new laboratory formulation was developed, LM06, increasing the calcium carbonate concentration to 8% of the core weight, and the cellulose amount was diminished accordingly.

A scale-up of the sixth laboratory formulation led to the first pilot batch PM01. The granulation of the pilot batch had similar results to the laboratory batch, rendering 64.5% granules in the range of 1000 – 300 µm.

The tableting process was carried at high speed, and the resulting cores had good pharmacotechnical properties. Also, a quantitative analysis of MSZ was carried out by HPLC (Figure 3).
In order to test the robustness of the granulation and tableting processes, other two pilot batches were produced. The process was reproducible (Table 2).

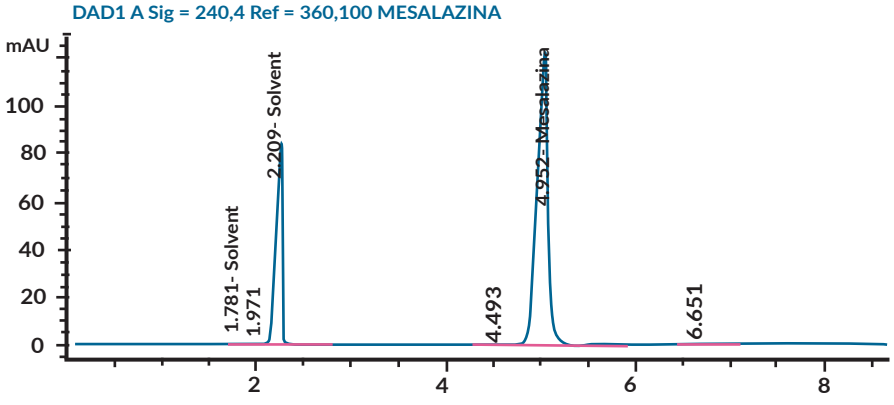

FIGURE 3. Mesalazine chromatogram

The controlled release of MSZ in the intestines can be achieved using gastro-resistant coating [14]. We employed an aqueous enteric acrylic system: Acryl-eze, weight gain PM01 8%, PM02 10%, PM03 12%. This system was successfully used combined with a hydroxypropyl methylcellulose base coat [15]. For all three pilot batches an Opadry base coat was used, weight gain 2.2%.

The first two batches failed to pass the gastro-resistance test. The results of the third pilot batch complied with all the requirements of this phase.

The dissolution profile of the new developed MSZ generic was compared to that of Salofalk® 500 mg gastro-resistant tablets, in order to preliminary asses therapeutic equivalence [16]. Experimental results of dissolution tests of PM03 MSZ 500 mg gastro-resistant tablets showed a 9.7% similarity factor to the original pharmaceutical product (Figure 4).

The gradual degradation of the coating film of all the tablets, with progressive release of the active substance, is observed approximately 5 minutes after the initiation of the dissolution process. The first sampling operation is performed at 15 minutes, at which point the film of all tablets is already completely dissolved. For the generic product of batch PM03 the active substance is released in a considerable proportion (78.00%), unlike the original product releasing a small amount of mesalazine (2.40%). The amount of active substance continues to increase for both products. The generic product releases the active substance almost completely

TABLE 2. Pharmacotechnical characteristics of mesalazine cores – pilot batches

		Batch		
Characteristic	Admissibility crietria	PM01	PM02	PM03
Average mass (mg)	800 ± 5% [760.0 - 840.0]	798.2	790.6	792.4
Hardness (N)	200-350	245	225	271
Thickness (mm)	6.3-6.5	6.3	6.4	6.3
Friability (%)	No more than 1%	0.16	0.15	0.15
Water (%)	Maximum 4%	1.66	1.70	1.68
Identification	IR spectrum according to the reference	Complies	Complies	Complies
	Retention time of the test solution similar to the standard solution	Complies	Complies	Complies
Assay (mg/tablet)	500 ± 5% [475.0 - 525.0]	505.7	492.3	492.8
Chemical related impurities (%)				
Impurity H	≤ 0.3	ND*	ND*	ND*
Impurity F	≤ 0.1	ND*	ND*	ND*
Impurity J	≤ 0.1	ND*	ND*	ND*
Impurity O	≤ 0.1	ND*	ND*	ND*
Impurity P	≤ 0.1	ND*	ND*	ND*
Impurity E	≤ 0.05	ND*	ND*	ND*
Impurity G	≤ 0.05	ND*	ND*	ND*
Impurity L	≤ 0.05	ND*	ND*	ND*
Impurity M	≤ 0.05	ND*	ND*	ND*
Impurity R	≤ 0.05	ND*	ND*	ND*
Other impurities	≤ 0.05	ND*	ND*	ND*
Total impurities	≤ 0.5	ND*	ND*	ND*
Impurity A and C (ppm)				
A: 4-aminophenol	≤ 200	ND*	ND*	ND*
C: 2-aminophenol	≤ 200	25.7	24.9	25.5
Impurity K (ppm)				
Aniline	≤ 10	ND*	ND*	ND*

*ND = Not detected

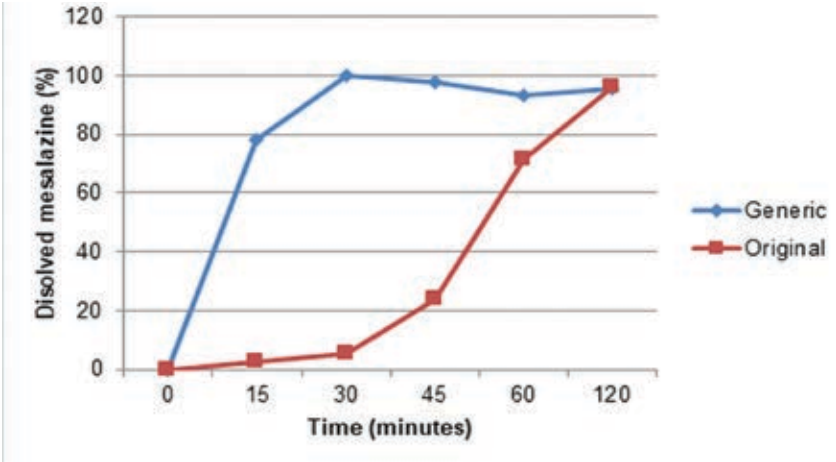

FIGURE 4. The dissolution profile of the generic product PM03 versus the original product

(99.70%) after 30 minutes of dissolution, unlike the original product which reaches the maximum MSZ concentration after 120 minutes. This immediate release of the API would suggest that the generic product could start to produce a therapeutic effect in a shorter amount of time compared to the original. After 15 minutes there is almost complete dissolution of the active substance in the generic product tablets.

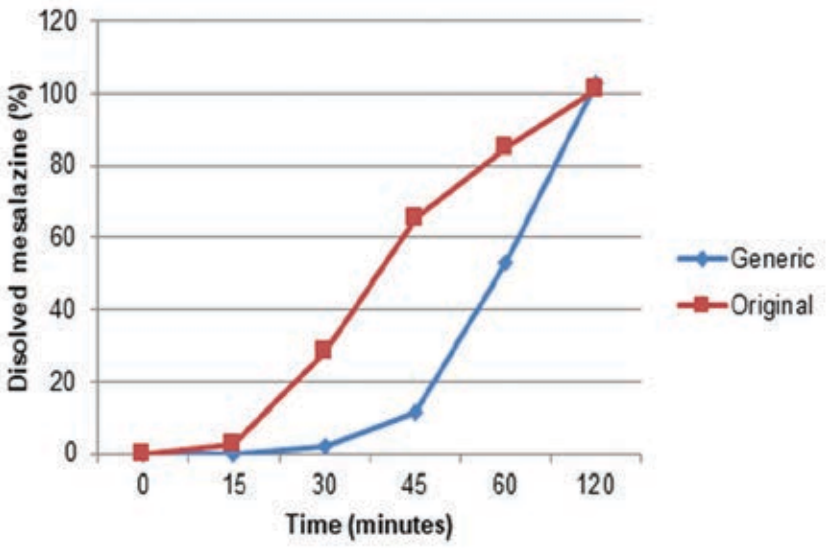

FIGURE 5. The dissolution profile of the generic product PM04 versus the original product

A first possible solution to reduce the speed of dissolution would be to decrease the super disintegrant quantity. For the formulation of pilot batch PM04 we applied a 50% reduction of croscarmellose sodium percentage compared to PM03, specifically 1.5% instead of 3%. Cellulose was used for weight correction. The similarity factor increased to 25.8% for MSZ gastro-resistant tablets batch PM04 (Figure 5).

Observing the allure of the curves of PM04, PM03 and the original product (Figure 4 and 5), a further development of this study would suggest testing superdisintegrant ratios in between the values of the two generics. Other possibilities to expand the study include variations of the granulation process [17] and variations of excipient ratio and type [18].

CONCLUSIONS

Mesalazine is the standard therapy of inflammatory bowel disease. Several research directions target the direct delivery of this substance to the intestine. A new formulation of MSZ 500 mg gastro-resistant tablets was developed. A new gastro-resistant tablets mesalazine formulation was developed by means of wet granulation, tableting (oblong tablets) and coating. Each step of the process was controlled, and the intermediary product was analyzed. Further studies to modulate the dissolution profile of the tablets are in progress.

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