

Preformulation and preliminary formulation studies of mesalazine gastro-resistant tablets

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ABSTRACT

Mesalamine, 5-aminosalicylic acid or mesalazine is the standard therapy of inflammatory bowel disease. A small number of pharmaceutical dosage forms with mesalazine are on the market.

The aim of this study was preformulation and preliminary formulation studies of oral gastro-resistant tablets containing 500 mg mesalazine. The reasons why a gastro-resistant tablet was chosen are: increased compliance of the patient, increased chemical stability and modified release modulation (mesalazine has a local effect on mucosa). The raw materials were of pharmaceutical grade. The following analytical techniques were involved: differential scanning chromatography (DSC), *in vitro* release, particle size determination, high performance liquid chromatography (HPLC). The compatibility of mesalazine with several excipients was tested using DSC. Wet granulation of mesalazine and starch showed that the fourth (LM04) formulation generates the highest amount (69.1%) of granules in the range of 1000–300 µm. Oblong tablets (pilot batches) were produced. The cores were coated with an enteric coating acrylic agent in order to achieve gastro-resistance. A new gastro-resistant tablets mesalazine formulation was developed by means of wet granulation, tableting (oblong tablets) and coating.

Keywords: mesalazine, gastro-resistant tablets, pharmaceutical development, wet granulation, gastro-resistant coating

INTRODUCTION

Mesalamine, 5-aminosalicylic acid or mesalazine is the standard therapy of inflammatory bowel disease. Ulcerative colitis and Crohn's disease are the main manifestation forms in this category [1]. Recent studies show a growth of the prevalence of the disease in recent years [2]. A small number of oral and rectal pharmaceutical forms containing MSZ are available,

individual doses between 250 mg and 2,000 mg [3,4]. Several research directions target the direct delivery of this substance to the intestine: formulation of multiparticulate systems (pellets coated with a polymer resulting in a pH dependent release system), formulation of composite materials (especially cross-linked chitosan with glutaraldehyde) [1,5-7].

The aim of this study was preformulation and preliminary formulation studies of oral gastro-resistant tablets containing 500 mg mesalazine. This pharmaceutical form was selected due to a couple of reasons. Oral pharmaceutical forms increase the compliance to the prescribed treatment [8] and gastro-resistant coating ensures both the protection against environmental destabilizing factors

such as light and oxygen and the controlled release of the active pharmaceutical ingredient [9].

MATERIAL AND METHODS

Materials

MSZ (Erregiere), microcrystalline cellulose (JRS Pharma), partially pregelatinized maize starch (Colorcon), povidone (BASF), magnesium stearate (Mosselman), lactose monohydrate (Meggle), croscarmellose sodium (FMC BioPolymer), colloidal silicon dioxide (Evonik), talc (Luzenac), calcium carbonate (Shangai Nuoceng Pharmaceuticals). All the components were of pharmaceutical grade and complied with the relevant monographs of the European Pharmacopoeia, 9th edition [10]. Coating system: Opadry clear (Colorcon), Triethylcitrate (Colorcon), Acryl-Eze (Colorcon). Also purified water (Ph. Eur., 2016) was used in the process.

Process steps and equipment – laboratory batches weighing – balance (Mettler Toledo), wet granulation - fluid bed granulator (Bosch), manual blending, tableting – eccentric press (Riva).

Process steps and equipment – pilot batches weighing – balances and scales (Mettler Toledo), wet granulation - fluid bed granulator (Bosch), blending – blender (Servolift), tableting – rotary tableting press (Fette 102i), oblong punch 18.2/7.7 mm, coating – coating equipment (O'Hara Technologies).

Methods

Differential scanning calorimetry (DSC): Netzsch calorimeter, model DSC 200F3 Maia. Oven DSC 200F3; aluminum sample pans, 40 mL/min

nitrogen, probe weight 7 mg, start temperature 30°C, end test temperature 400°C. The test was conducted for the active substance and the excipients, followed by the combinations active ingredient-excipient in a ratio of 1: 1.

Granulometry analytical sieve shaker Retsch AS 200, test time 4 minutes, 1 mm/g amplitude, 10 s interval, sieves 1 mm, 720 µm, 300 µm, 100 µm and 50 µm; 100 g mesalazine probe.

In process-control height, diameter and hardness tester – Erweka TBH 225 TD, friability tester – Erweka TDR 100, disintegration tester – Erweka TZ 72. The tests were conducted in accordance to compendial references [10].

Dissolution tests Agilent technologies 708-DS Dissolution Apparatus (rotating paddle). Dissolution media: 0.1 N clorhidric acid, residence time 120 minutes, followed by disodium hydrogen phosphate buffer pH 6.8 residence time 15, 30, 45, 60, 120 minutes. Identification and assay of MSZ and impurities High Performance Liquid Chromatography (HPLC): Agilent Technologies 1260 Infinity. The tests were conducted in accordance to compendial references [10,11].

For tablets assay, a Xterra MS C18 chromatographic column was used (25 cm × 4.6 mm, octadecylsilyl silica gel – 5 µm), mobile phase consisted of a 0.69% (m/w) solution of KH₂PO₄, adjusted to pH 6.2. Elusion was isocratic, flow rate 1 mL/min, temperature of the column was 40°C, detection UV at 240 nm.

RESULTS AND DISCUSSION

In order to obtain gastro-resistant tablets containing 500 mg MSZ,

several excipients were selected. The compatibility of the API with these excipients was tested using DSC (Figure 1).

A mixture ratio of 1:1 MSZ and each of the following: croscarmellose sodium, magnesium stearate, povidone showed a different profile compared to the individual behavior, however any of the mentioned excipients are employed in small quantities in oral solid dose formulations, the actual API:excipient ratio in this case being 1:0.05 (w/w), reducing the potential negative influence of the excipient. No interactions were revealed between mesalazine and Aerosil, starch, talc and lactose. A formulation containing MSZ, starch, croscarmellose sodium, magnesium stearate was agreed.

MSZ has poor flow capacity, rendering inefficient the process of direct compacting. The granulation of the API offers the possibility to significantly modify this inconvenient. It also prevents the components of the powder mixture from being separated; it improves the compression properties of the mixture by reducing the proportion of air between the particles and reduces the compressive force needed for tableting [12].

Four laboratory batches were developed LM01, LM02, LM03 and LM04. For the first laboratory batch wet granulation was performed using MSZ and starch, the ratio was 10: 0.5. For the second laboratory batch granulation was performed increasing the binder 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

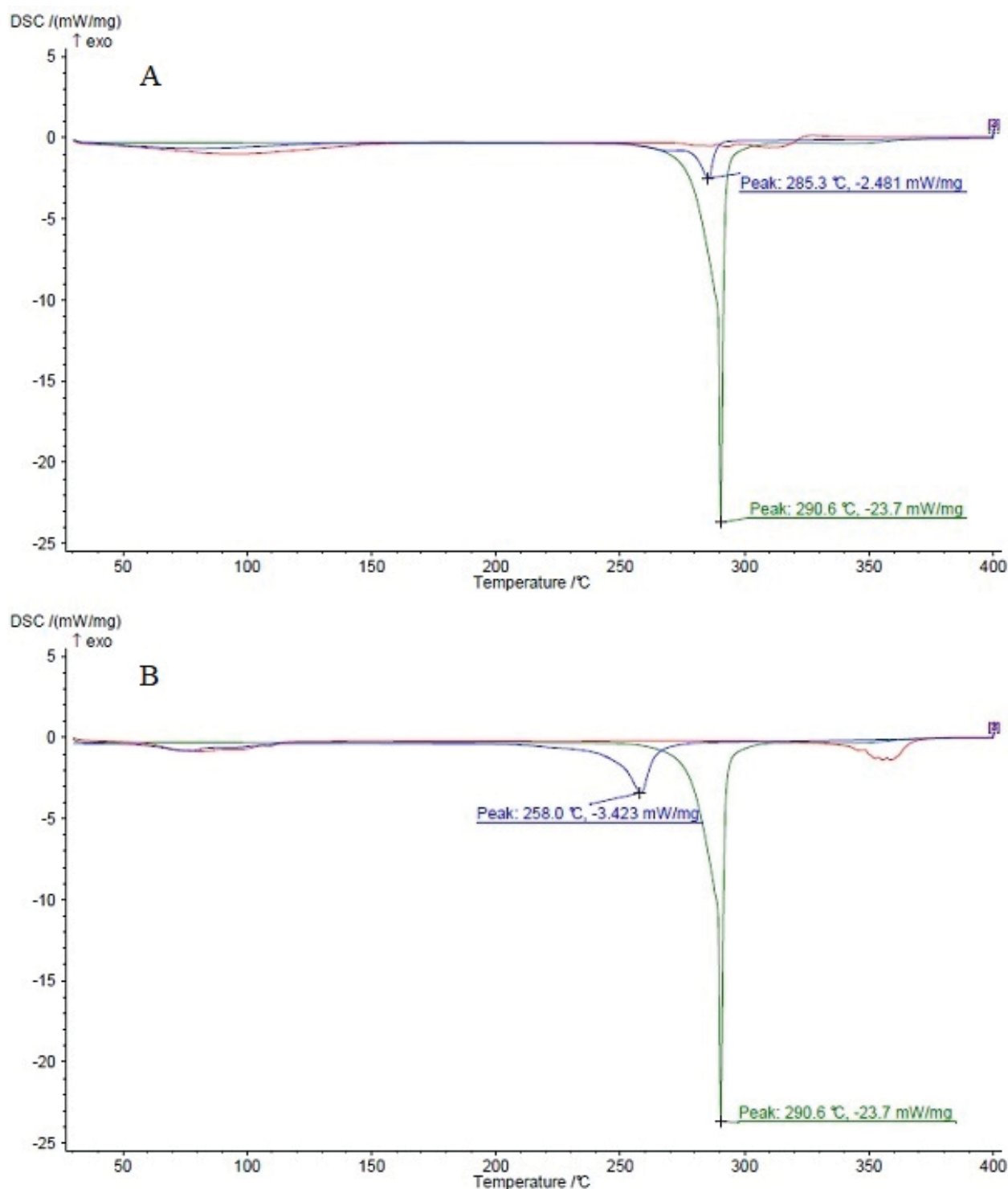


FIGURE 1. DSC analysis of mesalazine and excipients (A - Starch; B - Magnesium stearate; Mesalazine – green; Excipient – red and Mesalazine:Excipient 1:1 - blue)

TABLE 1. The composition of granule – laboratory batches

Raw material	Quality (mg/tablet)			
	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)

highest amount (69.1%) of granules in the range of 1000 – 300 μm .

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

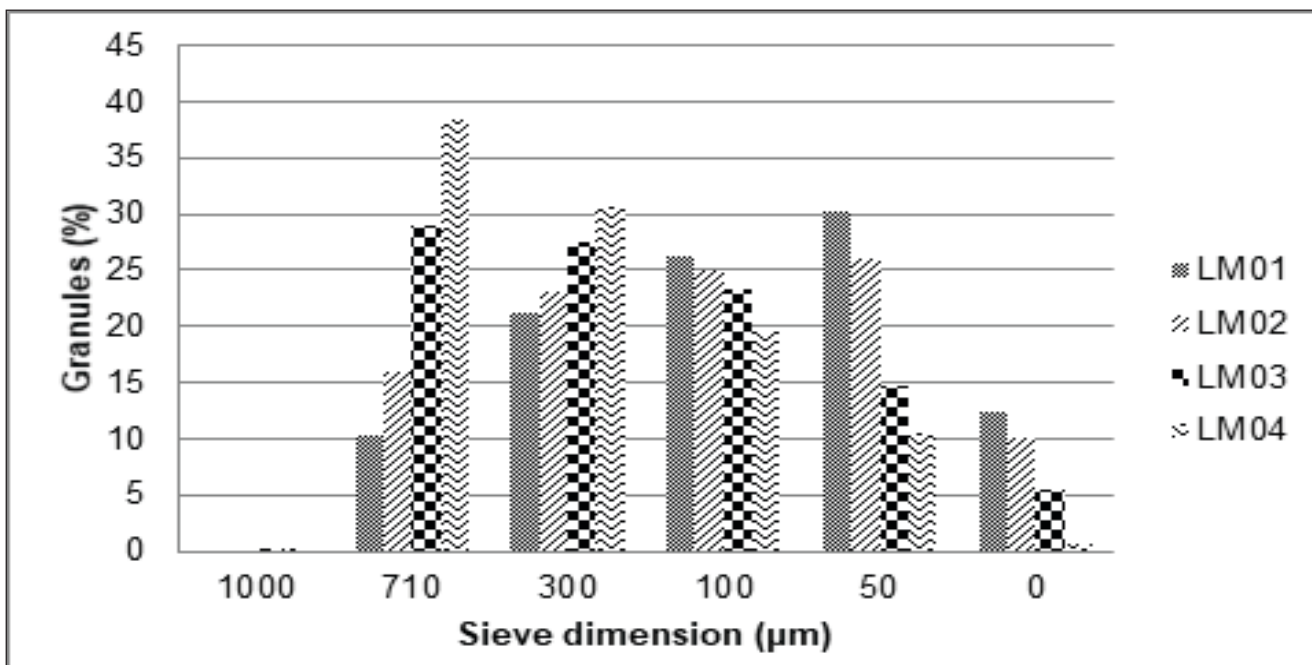


FIGURE 2. The granulometric distribution of mesalazine granules – laboratory batches

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).

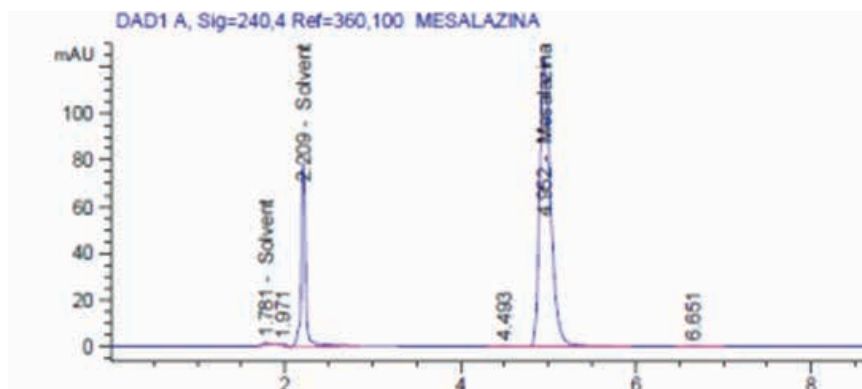


FIGURE 3. Mesalazine chromatogram

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 assess 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 (99.70%) after 30 minutes of dissolution, unlike

TABLE 2. Pharmacotechnical characteristics of mesalazine cores – pilot batches

Characteristic	Admissibility criteria	Batch		
		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

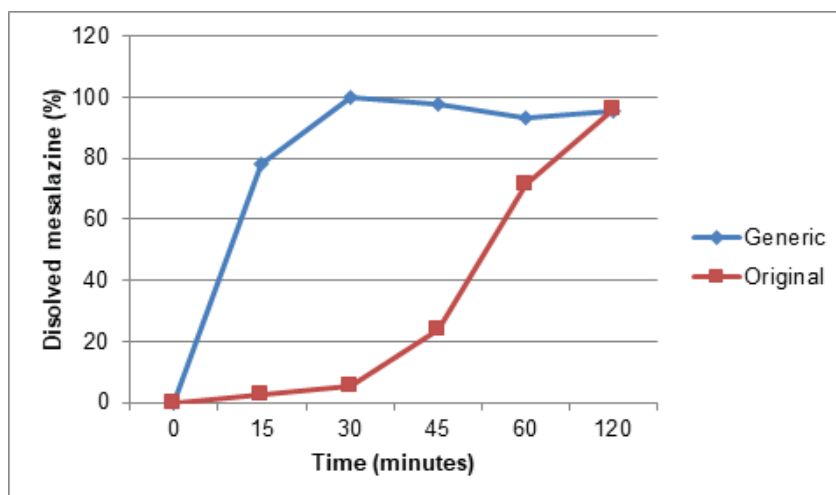


FIGURE 4. The dissolution profile of the generic product PM03 versus the original product

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.

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

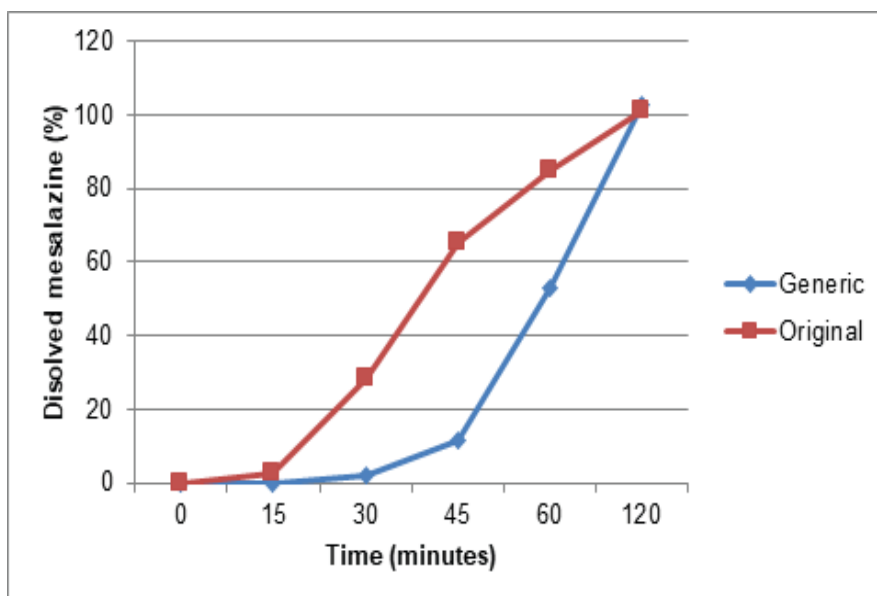


FIGURE 5. The dissolution profile of the generic product PM04 versus the original product

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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