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# Qualitative evaluation of oral solid dosage forms containing Mesalamine

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**Abstract:** Mesalamine is an anti-inflammatory drug used in the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. In contrast to the immediate-release oral solid dosage forms, mesalamine should exhibit delayed release achieved through an enteric coating intended to resist gastric fluid and release the drug into the colon region. The lack of application of the coating as well as the guarantee of the quality of the coating may result in aggravation of the disease due to the lack of desired therapeutic effect, since the drug may undergo dilutions prior to reaching the target. The objective of this study was to evaluate qualitatively the essential basic properties of oral solid dosage forms containing 800 mg of mesalamine produced in compounding pharmacies, identified as M1, M2 and M3, comparing them with the following pharmaceutical products: reference medicine (R) and generic (G). Samples were submitted to visual analysis and weight variation and disintegration tests. The results obtained in relation to the visual aspect and the tests related to weight were satisfactory for all the samples. On the other hand, the evaluation of the enteric performance was unsatisfactory for the samples M1 and M2, while the samples M3, R and G were approved in the acid and basic stages of the disintegration test. Thus, it may be inferred that compounding pharmaceutical establishments in Brazil have found difficulties in fulfilling the specifications necessary for mesalamine to reach the colon region, indispensable for its pharmacological effect. **Keywords:** mesalamine, capsules, disintegration, colon delivery, quality control, inflammatory bowel disease.

## Introduction

The incidence of inflammatory bowel diseases (IBD) is rising worldwide, increasing the burden on patients and the health care system; in 2016, this pathology affected around 1.6 million Americans with as many as 70,000 new cases diagnosed each year [1-2]. Crohn's disease (CD) and ulcerative colitis (ULC) are the most common types of IBD, characterized by inflammation and ulceration of the gastrointestinal (GI) tract. ULC primarily attacks the large intestine, whereas CD is characterized by periods of clinical remission alternating with periods of relapse reflected by recurrent clinical symptoms, and can affect the whole digestive system from the mouth to the anus and also other sites such as skin, eyes and joints [3]. The symptoms of IBD, usually debilitating, are present in the form of recurrent diarrhea, rectal bleeding, vomiting and anorexia, producing an adverse effect on patients' social, professional, academic, family and sexual relationships [4].

Currently there is no cure for IBD, thus the basic aim is still to make the best use of conventional treatments based on IBD pathophysiology [1]. The treatment consists of achieving and maintaining the remission of inflammatory episodes to alleviate the symptoms [5].

Aminosalicylates are commonly listed as the first choice among the main therapeutic agents used in the treatment of these patients from systems capable of ensuring that the active principle does not dilute along the GI tract and reach local levels in the inflamed mucosa [6]. In this sense, mesalamine, also known as 5-aminosalicylic acid (5-ASA) or mesalazine, constitutes effective and well-tolerated first-line therapy in mild to moderate acute intestinal disease, as well as for long-term maintenance treatment in patients with ULC [7]. Mesalamine acts locally on the inflamed intestinal tissue in the acute phase and in the prevention or reduction of relapses of these diseases, such as colitis, ulcerative proctitis and CD. It is also indicated for the symptomatic treatment of diverticular disease of the colon, associated or not with antibiotic therapy such as ampicillin, sulbactam or rifaximin. Its mechanism of action is probably due to inhibition of prostaglandin and leukotriene synthesis in the gastrointestinal mucosa [7-8].

In a systematic review, Nakase commented on the ability of mesalamine to induce remission of active proctitis and distal colitis in 31 – 80 % (median, 67 %) of patients compared to 7 – 11 % of patients treated with placebo, in a meta-analysis evaluating 11 trials with a total of 778 patients [9]. In Brazil, there are several pharmaceutical dosage forms of mesalamine available, as follows: suppository (250 and 500 mg), coated tablet (400, 800 and 1200 mg) and hard capsule, the latter being a compounding product. Sweetman reports that oral administration of mesalamine from conventional formulations is primarily absorbed in the upper GI tract, leaving little of the drug reaching the colon. Therefore, oral preparations are usually formulated to release the active principle into the terminal ileum and into the colon where local effect is expected. Even in delayed-release preparations, it is believed that 30 to 50 % of an oral dose is lost to absorption in healthy individuals [8].

Delayed-release pharmaceuticals also referred to as enteric-coated or delayed-release (enteric-coated), unlike those of immediate release, are intended to resist gastric fluid and release the active principle into the intestinal fluid [10-11], being also different to controlled release dosage forms. In capsules and tablets, a polymeric coating called enteric or gastro-resistant is applied which ensures this delay [12]. An enteric coating may be based on the time required for the tablet or capsule to transit the stomach and may delay dissolution through a coating of suitable polymeric thickness or material. It can also be developed based on pH, so that the core resists dissolution in highly acidic medium and dissolves easily in pH equal to or greater than 4.80 [13].

Different materials have been used in the preparation of delayed-release pharmaceutical oral solid dosage forms, among them, pH-sensitive polymers, commercially available for the production of this type of specific pharmaceutical form, such as cellulose acetate phthalate (phthalic anhydrite polymer and acetate ester of cellulose); cellulose hydroxypropylmethyl ether polymer; copolymer methyl vinyl ether and maleic anhydride; polymer derived from acrylic acid crosslinked by divinylglycol; and polymers derived from methacrylic acid with butyl methacrylate, trimethylammonium methacrylate hydrochloride, or ethyl dimethylaminomethacrylate [14-17].

It is known that several approaches have been used in the development of colon-specific drug delivery systems such as the use of formulation components that interact with different aspects of GI physiology to achieve colon targeting, for example chemically modified polymers that influence the extent of enzymatic degradation [18]. This context explains why the most commonly used dosage forms containing mesalamine are modified-release formulations, since these formulations use strategies for colonic release by the employ of insoluble and/or pH-sensitive polymers [19]. In contrast, sustained release (SR) oral solid dosage forms, also known as prolonged action, sometimes labeled as extended-release (XR), are those which allow at least a reduction in the frequency of dose when compared to the available drug in the form of immediate-release [10].

The pharmaceutical compounding segment has undergone profound transformations that aim at meeting the quality precepts inherent to the drug, process management, and quality assurance system [20] in order to achieve the pharmacotherapeutic purpose. Pharmaceutical preparations should follow the requirements set forth in the Resolution of the Collegiate Board of Directors (RDC) N. 67, of October 08, 2007, of the National Sanitary Surveillance Agency (ANVISA) in Brazil, which provides for Good Practices in Manufacturing Compounding and Officinal Preparations for Human Use in Pharmacies, which focuses on

the handling, preservation and dispensing of compounding, official preparations, as well as for the acquisition of raw materials and packaging materials [21].

Considering that the Mesacol® coated 800 mg tablet (Takeda Pharma Ltda., Brazil) can cost up to three times as much in comparison with the compounded formulation of mesalamine 800 mg capsules, the request of this type of compounding preparation becomes a viable alternative for the oral treatment of IBD. However, despite this advantage in relation to the industrialized medicine, there are numerous obstacles that hinder the growth of the compounding segment, the biggest one being the lack of credibility of the product compounded by the absence of strict quality control [22]. In this sense, the present work had as its objective to evaluate the quality of the oral solid dosage forms containing mesalamine, applying physical methods by way of weight variation and disintegration assessment.

**Material and Methods**

Among six (06) compounding pharmacies existing in a city in the interior of Minas Gerais state, Brazil, only three (03) establishments prepared the oral dosage form requested as enteric capsules containing 800 mg of mesalamine. The others claimed not to carry out this type of preparation.

Thus, mesalamine hard capsules (n = 30) were prepared in three compounding pharmacies from May to October 2018, denominated M1, M2 and M3. In parallel, industrialized products such as the reference pharmaceutical product, known as Mesacol® 800 mg coated tablets (expiration date: Aug, 2019), which has been designated as "R" and also the generic pharmaceutical product (expiration date: Oct, 2019), named "G" were analyzed in the present study.

Disintegration media were prepared using reagents of analytical grade, as follows: hydrochloric acid and sodium hydroxide were purchased from Isofar, (Duque de Caxias, Brazil); potassium phosphate monobasic anhydrous and phosphoric acid were obtained from Synth, (Diadema, Brazil); and freshly distilled water was produced by a Distillation Machine, model BD1 DL (Biopar, Brazil).

*Label analysis*

Analysis of the labels was carried out to verify that they and their respective packaging were in accordance with item 12.1 of Annex I and item 12.3 (required) of Annex VII described in RDC 67/07 [21]. In this sense, the following information should be stated: name of the prescriber, patient's name, registration number of the formulation in the prescription book, date of preparation, expiration date, formulation components with respective amounts, number of units, weight or volume contained, dosage, pharmacy identification, national register of legal entity, full address, name of the pharmacist holding the Regional Pharmacy Council registration number.

*Physical analysis*

The physical characteristics of samples M1, M2 and M3 were visually analyzed taking into account their physical appearance [23]. It was observed whether the capsule size corresponded to the desired size. In the case of a clear capsule, the uniformity of the mixture, the powder particle size and the capsule filling were checked. In addition, the integrity of the capsules was analyzed for absence of cracks, creased regions, softening, staining and color uniformity. Finally, the number of capsules was counted to check compliance with the label.

*Weight variation*

The test of weight variation for compounding hard gelatin capsules (M1 – M3 samples) was performed according to the procedure described for *Determination of weight in capsules obtained by the compounding process* available in the Brazilian pharmacopeia national formulary [24]. In order to do so, three parameters were evaluated using n = 10 as follows: average weight of the compounded hard capsules applying the variation limits of ± 7.5 %, relative standard deviation (RSD) lower than 4 % and variation of theoretical content (VTC) between 90 – 110 %.

The weight variation of the coated tablets (R and G samples) was performed according to the Brazilian pharmacopeia [25] by applying n = 20 and the variation limits of ± 5 %. Results were expressed as the arithmetic mean of the values and standard deviation ($\bar{X}$±SD) by using Microsoft® Office Excel version 2016.

*Disintegration test*

Disintegration of oral solid dosage forms (n = 6) is a qualitative assessment and was performed using a Disintegrator Ethik Technology Model 301. One dosage unit was placed in each of the six tubes of the basket, under the action of the disks using the immersion fluid indicated by the pharmacopeia.

The delayed-release hard capsules (M1, M2 and M3 samples) were subjected to the procedure described in the Brazilian pharmacopeia for *Enteric-coated tablets or capsules (gastro-resistant)* and were considered approved after two disintegration steps, as follows: (1) acidic (hydrochloric acid 0.1 mol/L as simulated gastric fluid) and (2) basic (pH 6.8 phosphate buffer 0.05 mol/L), maintained at 37 ± 1 ºC, tolerating 60 minutes in the first and disintegrating completely in less than 45 minutes in the second. Hard capsule shells (uncoated) should be disintegrated within 45 minutes in water at 37 ± 1 ºC [25].

The coated tablets (R and G samples) were subjected to the disintegration procedure, using the dissolution conditions described in USP 37 for *Mesalamine Delayed-Release Tablets*, and are considered approved after following three stages: (1) acidic (simulated gastric fluid), (2) basic 1 (pH 6.0 phosphate buffer) and (3) basic 2 (pH 7.2 phosphate buffer), tolerating 120 minutes in the acid stage, 60 minutes in basic stage 1 and completely disintegrating in less than 90 minutes in basic stage 2. All stages were maintained at 37 ± 0.5 °C and under the action of the disks [26]. Film-coated tablets for immediate-release should disintegrate in water or simulated gastric fluid at 37 ± 1 ºC within 30 minutes [25].

**Results and Discussion**

Mesalamine is light brown to pink, lightly water-insoluble, practically insoluble in alcohol, its soluble crystals are soluble in dilute solutions of alkaline hydroxides and dilute solutions of hydrochloric acid. It displays a melting range between 260-280 °C; has two pKa of 2.3 and 5.69; its molecular mass is 153.12 g/mol, and its molecular formula is $C_7H_7NO_3$ [27].

As previously related, mesalamine should be available the terminal ileum and the colon where the local effect is expected. Thus, it is essential that conventional oral dosage forms present characteristics of a colon-specific drug delivery system [8]. In agreement to the above approach it becomes imperative that the compounding hard capsules containing mesalamine be carried out using capsule shells capable of ensuring this kind of performance. In parallel, it was observed that the M1 – M3 samples were labeled in accordance with the current norm [21].

Visual analysis of the medicine is an important quality test, the main purpose of which is to evaluate the physical and aesthetic integrity of the product. The physical analyzes are basic observational tests necessary for the beginning of the identification of a pharmaceutical product, but are not conclusive and other concomitant tests are necessary [28]. It was noted that M1 – M3 samples were prepared in colorless to slightly yellowish hard capsules of size No. 00, i.e. of 0.95 $cm^3$ capacity. In contrast to the others, M3 also had the following inscription on the shells: "Caps Acid Resistant". Additionally, all exhibited conformity to the uniformity of the powder mixture. The capsules were found to be integral and locked, that is, without cracks, crumpled regions, softening or staining; clean and with the exact amount of capsules described on the label.

The three compounding pharmacies in the present work provided the capsules at the dosage of 400 mg due to the high requested dosage (800 mg) coupled with the poor flow properties of the drug (Hausner index; Carr index). Thus, all pharmacies prepared twice the number of capsules, i.e., two 400 mg capsules to complete the 800 mg dose. The results of the weight variation and related parameters are presented in Table 1, which shows that all medications were approved for weight-related criteria, as they were within the variation limits as follows: ± 7.5 % for M1 – M3 samples, and ± 5 % for R and G samples, RSD lower than 4 % and VTC between 90 and 110 %.

Table 1: Evaluation criteria in relation to weight determination of oral solid dosage forms containing mesalamine.

| Sample | Average weight (mg) | Variation limits (mg) | RSD (%) | VTC (%) |
|---|---|---|---|---|
| **M1** | 525.9 ± 15.5 | 486.5 – 565.4 | 2.9 | 94.9 – 103.6 |
| **M2** | 518.7 ± 15.0 | 479.8 – 557.6 | 2.9 | 94.2 – 103.9 |
| **M3** | 592.9 ± 12.6 | 548.4 – 637.3 | 2.1 | 96.8 – 103.5 |
| **R** | 1108.5 ± 25.6 | 1053.1 – 1163.9 | 2.3 | * |
| **G** | 1076.2 ± 8.0 | 1022.4 – 1130.0 | 0.7 | * |

Source: survey data. RSD = relative standard deviation. VTC = variation of theoretical content. *Parameter not applied to industrialized medicine.

VTC allows an estimation of the acceptable variation of the capsule weight, assuming that the encapsulated powder mass is homogeneous. Thus, according to the Good Manufacturing Practices, with regard to the mixture of powders, it can be inferred that the amount of drug is uniformly distributed between the capsules prepared in the pharmacies (M1 – M3 samples) and analyzed in this work (Table 1). It is worth mentioning that dispensing a failed set of weight determination criteria could result in an inadequate distribution of the encapsulated composition (active pharmaceutical ingredient and excipient), interfering significantly with the concentration of drug, in mg, present in the capsules [29]. This could lead to insufficient or excessive drug dosage episodes because, according to the American Pharmacopoeia, oral solid dosage forms containing mesalamine ($C_7H_7NO_3$) should show 90 to 110 % of the reported dose of $C_7H_7NO_3$ in their dosage units [26]. Table 2 shows the qualitative composition and relative contribution of the powders considering the reported dose of mesalamine and the internal contents present in the capsule shells (M1 – M3 samples), or in the tablet weight (R and G samples).

Table 2: Composition of excipients and relative contribution of powders found in oral solid dosage units constituted by mesalamine.

| Sample | Composition of the excipient | Relative contribution of powders % (m/m) |
|---|---|---|
| **M1** | Corn starch, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, lactose monohydrate and sodium lauryl sulfate | 99.1 % Mesalamine<br>0.9 % Excipient |
| **M2** | Absent | 100.0 % Mesalamine |
| **M3** | Microcrystalline cellulose, silicon dioxide, magnesium stearate and talc | 84.6 % Mesalamine<br>15.4 % Excipient |
| **R** | Sodium starch glycolate, triethyl citrate, copolymer of methacrylic acid and methyl methacrylate, silicon dioxide, magnesium stearate, lactose monohydrate, macrogol, yellow iron oxide, red iron oxide, povidone and talc | 72.2 % Mesalamine<br>27.8 % Excipient |
| **G** | Purified water, isopropyl alcohol, pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, dusk yellow lacquer aluminum dye 6, titanium dioxide, magnesium stearate, lactose monohydrate, macrogol, red iron oxide, methacrylic acid anionic polymer, non-ionic polymer of methacrylic acid, talc and triethylcitrate | 74.3 % Mesalamine<br>25.7 % Excipient |

Source: survey data.

It can be seen in Table 2 that the tablets have the following coating agents: copolymer of methacrylic acid and methyl methacrylate in the R sample; and anionic polymer of methacrylic acid and non-ionic polymer of methacrylic acid in the G sample, responsible for the achievement of gastro-resistant behavior, besides being constituted by approximately 26 to 28 % of excipients. Banakar reports the importance of selecting excipients in the performance of oral solid dosage forms, since depending on the amount added to the formulation, the quality, or function of the formulations, it is possible to interfere with oral bioavailability affecting therapeutic efficacy [30].

In this sense, it could be observed that the compounding pharmacies in the present work employed around 1 % and 15 % of excipient in the filling of the mesalamine capsules for the M1 and M3 samples, respectively; while in M2 there is no excipient. However, none of the capsules (M1, M2 and M3) comprise adjuvants capable of promoting enteric release. Evidently the desired biopharmaceutical performance range, i.e., delayed release capsules, should be met, based on the use of capsule shells marketed as acid resistant by the suppliers. Finally, the results of the disintegration test are shown in Table 3.

Table 3: Evaluation of the disintegration of oral solid forms containing mesalamine.

| Sample | Acid stage | Basic stage | Result |
|---|---|---|---|
| **M1** | Disapproved | N.A. | Disagree |
| **M2** | Disapproved | N.A. | Disagree |
| **M3** | Approved | Approved | Agree |
| **R** | Approved | Approved | Agree |
| **G** | Approved | Approved | Agree |

Source: survey data. N.A. = not applicable.

As previously mentioned, oral solid dosage forms containing mesalamine should disintegrate in the more favorable GI environment, particularly in the colon, to make the drug available to biological fluids, ensuring success in pharmacotherapeutic treatment [8]. The disintegration test is useful for assessing the quality of both gastro-resistant capsules as well as enteric-coated tablets, excluding immediate-release hard capsules filled with coated drugs [25], such as omeprazole pellets.

It is known that the coating of tablets prevents the degradation of mesalamine in the upper digestive tract allowing the release of drug only in the ileum and colon, where the pH is above 7. Approximately 75 % of the orally administered dose is not absorbed, being eliminated with the feces unchanged, and is thus available to act locally as an anti-inflammatory [7]. The capsules identified as M1 and M2 did not support 60 minutes at acid pH and were not referred to the basic stage. In this sense, the dosage forms M1 and M2 were found to be in disagreement with the expected results and were disapproved in the disintegration test (Table 3). Analogously, a study composed by Sant'anna & Freitas, also found unsatisfactory results when evaluating the quality of gastro-resistance. Samples of 50 mg diclofenac sodium capsules prepared by compounding pharmacies in São Paulo state, Brazil, were disallowed in the disintegration test described in Brazilian Pharmacopeia for *Enteric-coated tablets or capsules (gastro-resistant)* [31].

Although not establishing a correlation with *in vivo* behavior, it is understood that a delayed-release oral solid dosage form that fails the disintegration test will probably not be effective, i.e. will not achieve the desired therapeutic effect. Recently an *in vitro* assessment for several commercial modified-release mesalamine formulations was conducted. It was found that all four enteric-coated formulations were resistant to acid. In the intestinal phase of the test, release from the enteric-coated products was dependent on the nature of the pH-dependent coating material. For all the enteric-coated products, drug release was initiated in the small intestinal phase of the test and then continued in the colonic milieu of the test [19].

Based on Table 3, samples identified as M3, R and G presented satisfactory results in the disintegration stages (acid and basic). These results corroborate with those of Goyanes *et al*. [19]. Table 3 also displays that only one of the pharmacies (1/3) selected a

composition of 15.4 % of an excipient which is quantitatively adequate for mesalamine, in addition to correctly locking the acquired capsule shells with appropriate characteristics to obtain the desired behavior, i.e. enteral release in pharmacopoeial agreement.

In parallel, the role of suitable suppliers of enteric capsule shells is decisive, i.e. for delayed-release performance, as a primary raw material to achieve this type of release for several pharmaceutical forms containing the following drugs: mesalamine, sulfasalazine, bisacodyl, ammonium chloride, diclofenac sodium, didanosine, dirithromycin, divalproex, duloxetine, erythromycin, fluoxetine, naproxen, among others [26].Considering the importance of the quality control of the compounded pharmaceutical products, the results found point out the need for a more extensive monitoring of the compounding process. Therefore, a revision of sub-paragraph 9.2.3 of the resolution in question is suggested [21] which states: *"Analyzes of assay and uniformity of content of the active pharmaceutical ingredient of formulas whose pharmaceutical unit contains drug(s) in quantities of 25 milligrams or less, giving priority to those containing drugs in quantities of five milligrams or less"*, as this leads to an oversight over formulations with dosages above 25 mg of drug(s). Additionally, the need for specific dosage forms such as delayed-release hard capsules, will be evaluated against compliance with pharmacopoeial requirements, and finally, be employed effectively and safely in pharmaceutical compounded preparations.

It is worth noting that the neglect of the current norms puts the health of numerous patients at risk, which can lead from therapeutic inefficiency, in the case of reduction of bioavailability, to the increase of adverse and toxic reactions, leading in extreme cases to death.

## Conclusion

In conclusion, it is understood that although the modified-release of mesalamine from capsule shells and tablets is necessary to reach the colon region, compounding establishments have found difficulties in meeting this requirement, whether for operational or technical reasons, as well as the challenging issue of acquiring mainly enteric shells as raw material, since the suppliers provide acid-resistant hard capsule shells, which are not always adequate for delivering mesalamine into the terminal ileum and into the colon to act locally as an anti-inflammatory.

## Conflict of Interest

The authors report that they do not have any conflicts of interest.

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## Contribution of the Authors

B.C. Oliveira purchased, performed most of the tests, produced the tables, interpreted and discussed the results, and also wrote the text. G.C.P. Nascimento prepared disintegration media and partially performed the disintegration tests. A.J.P.S. Gomes was responsible for the orientation of this work and improved the manuscript.

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