

Development of mesalazine pellets coated with methacrylic-derived polymer

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Mesalazine (5-ASA) is the standard drug for the treatment of inflammatory bowel disease (IBD) due to its local effect on intestinal and colonic mucosa. The effective and safe treatment of this disease requires more efficient delivery of the active substance to its site of action. The focus of this study was the use of multiparticulate systems, a modified release form in which the drug is divided into several functional subunits of release in the form of granules or pellets. When these forms are administered, they are rapidly disintegrated, distributing their content throughout the gastrointestinal tract. The aim of this study was to develop and evaluate a multiparticulate system consisting of pellets coated with polymer for pH-dependent release, derived from methacrylic acid and incorporated into the tablet dosage form of mesalazine as a model drug. The extrusion-spheronisation technique was used, resulting in smooth and spherical pellets with uniform size distribution, which were coated in fluidized bed using Opadry[®] Enteric 94K28327 containing Eudragit[®] S100 as the agent regulating drug release. The dissolution profile of coated pellets showed good control of drug release from the polymer at the two levels of coating evaluated (8% and 10%), but only the 10% coated pellets were statistically similar to Asalit[®] 400 mg.

Uniterms: Mesalazine. Coated pellets/evaluation. Coated pellets/dissolution profile. Extrusion-Spheronisation/pellets obtention. Drugs/modified release.

A mesalazina (5-ASA) tem se apresentado como fármaco padrão para o tratamento da doença inflamatória intestinal (DII) devido ao seu efeito local na mucosa intestinal e colônica. A terapia efetiva e segura desta doença requer a chegada da substância ativa ao seu local de ação com maior eficiência. Nessa busca, tem se destacado o uso de Sistemas Multiparticulados, forma farmacêutica de liberação modificada, em que o fármaco está dividido em várias subunidades funcionais de liberação, sob a forma de grânulos ou péletes, que quando administrados, são rapidamente desintegrados distribuindo seu conteúdo por todo trato gastrointestinal. Este trabalho teve como objetivo desenvolver e avaliar péletes revestidos com polímero de liberação pH-dependente, derivado do ácido metacrílico, tendo como fármaco modelo a mesalazina. A técnica de extrusão-esferonização foi utilizada obtendo-se péletes lisos e esféricos com distribuição granulométrica uniforme, que foram revestidos em leito fluidizado utilizando Opadry[®] Enteric 94K28327 contendo Eudragit[®] S100 como agente regulador da liberação do fármaco. O perfil de dissolução dos péletes revestidos demonstrou bom controle na liberação do fármaco por parte do polímero nos dois níveis de revestimento avaliados (8 e 10%), porém, apenas os péletes revestidos a 10% demonstraram semelhança estatística com o medicamento de referência Asalit[®] 400 mg.

Unitermos: Mesalazina. Péletes revestidos/avaliação. Péletes revestidos/perfil de dissolução. Extrusão-esferonização/obtenção de péletes. Fármacos/liberação modificada.

INTRODUCTION

Inflammatory bowel disease (IBD) denotes a group of diseases that primarily affect the small and large in-

testines, and is characterized as chronic inflammation of unknown etiology. IBD is subdivided into ulcerative colitis (limited to the colon) and Crohn's disease (can affect any part of gastrointestinal tract from the esophagus to the anus but more often involves the small intestine and colon) (Cotran, Kumar, Robbins, 2000; Chuong, Christensen, Ayres, 2008).

Mesalazine (5-ASA) is used as the standard drug

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for the treatment of inflammatory bowel disease due to its local effect on intestinal and colonic mucosa and to its few side effects (Cai *et al.*, 2003; Qureshi, Cohen, 2005). Despite being the focus of many studies, mesalazine's mechanism of action is only partially understood, although it is accepted that its effect occurs locally in the intestinal mucosa by inhibiting cyclo-oxygenase and lipo-oxygenase, thus decreasing the production of prostaglandins and leukotrienes. The drug is also believed to act as a scavenger of free radicals, produced in greater numbers in patients with inflammatory bowel disease (USP-DI, 2007).

Pharmaceutical Technology has played a fundamental role in the investigation of systems that efficiently deliver the drug to its site of action. The focus of this study was the use of multiparticulate systems, modified-release form in which the drug is divided into many release subunits in the form of granules or pellets that can be incorporated into hard gelatin capsule or compressed forms (Collet, Moreton, 2005).

Pellets are spheres measuring between 500 and 1500 μm in diameter with applications in both the pharmaceutical and fertilizer industries. Pellets have several technological and therapeutical advantages such as optimum flow properties, narrow particle size distribution, surface-susceptible coating film offering enteric protection or controlled release, and wide dispersion in the gastrointestinal tract. This serves to reduce tract irritation by gastro-irritant drugs and lower the risk of adverse effects due to overdose (Santos *et al.*, 2004).

Among the techniques employed for preparing pellets, extrusion-spheronization has gained special attention because of its easy of application and resultant pellets with highly uniform particle size distribution which can be coated or compressed, yielding cores for subsequent polymer coatings able to control the drug dissolution process (Villar-Lopez *et al.*, 1999; Krogars *et al.*, 2000; Gupta *et al.*, 2001).

The use of a multiparticulate system for drug delivery in preference to a monolithic system was proposed by Hardy *et al.* (1985), after demonstrating that the units of the multiparticulate system were able to reach the colon quickly and be retain there for a long period of time. Due to the smaller particle size of multiparticulate forms compared to monolithic forms, multiparticulate systems are able to disperse more easily through the gastrointestinal tract, promoting more uniform and safe drug absorption.

The aim of this study was to develop a multiparticulate system containing mesalazine pellets coated with pH-dependent methacrylic derived polymer, with further characterization and evaluation of the drug release profile in vitro compared with the reference product. This was

achieved by using a dissolution medium that simulates changes in pH of the gastrointestinal tract, in a bid to obtain a feasible strategy for the development of therapeutic systems that release the drug at the colon.

MATERIALS AND METHODS

Production of pellets

Mesalazine anhydrous (40%w/v) (Deg, batch IF080303) and Microcrystalline Cellulose 101 (60%w/v) (Microcel[®] 101, Blanver; batch 208/06) were mixed and added to an aqueous solution of PVP-K30 (10%w/v) (Luviskol[®] K 30, BASF) to form a mass with plastic characteristics, which was then passed through an extruder (local development) mesh of 1 mm in diameter. The extrudate was spheronised (spheroniser Caleva M120) using a disk 12 cm in diameter (cross-hatch type) at 1000 rpm/10 min. The pellets were dried in a conventional hot-air oven Fabbe 201 (Sao Paulo, Brazil) at 40 °C for 24 hours.

Sample preparation

The pellets were classified by a set of sieves (0.5 mm, 0.710 mm, 1.00 mm and 1.4 mm). The size fraction 0.7 mm - 1.0 mm was separated into two batches of samples, denominated uncoated pellets (UC) and pellets for coating (C).

Coating of drug pellets

The sample (C) was coated in fluidized bed (LM-FBD Labmac 5.0 - inlet temperature of air and pellets of 40 °C) and the spray rate was 2.5 mL/min. The coating solution (8%w/v) was prepared using a mechanical shaker (Fisaton 713) at 90 rpm for 30 minutes. The coating was applied with two levels of weight gain (8% and 10%) at the end of the coating process.

Pellet friability

The friability was evaluated in a friabilometer (Erweka GmbH, Bizen, Germany) as described by Thoma, Ziegler, 1998.

Shape analysis of pellets (e_r)

The determination of particle shape (perimeter, maximum, minimum and mean diameters were used in determining the sphericity or shape factor e_r as described by Podczeczek *et al.*, 1999) and the ratio radius of the sam-

ples from the same batches was carried out by a black and white CCD video camera (Biocam-VI-6633-China) attached to a stereomicroscope Tecnival SQZ-SD4 (China). The scanned images were processed by Image Pro-Plus® software (version 1.2 Media Cybernetics, Silver Spring, MD, USA).

Drug content in pellets

The content of mesalazine for UC, C8 and C10 was determined (sample of 100 mg) by ultraviolet spectroscopy (UV-1601 UV-Visible Spectrophotometer Shimadzu) at 302 nm.

Coating Level

The coating level of each batch (C8 and C10) was calculated by subtracting the content of respective mesalazine in coated pellets, from that found for uncoated pellets (Amighi, Moes, 1996).

Production of multiparticulate systems

Two multiparticulate systems were prepared (M8 and M10) in the form of tablets, on pellets from the C8 and C10, respectively, associated with microcrystalline cellulose 101 (ratio of 1:1) as buffer and protective agent of the coating. For each system, the individual components were weighed and the mixture compressed in a hydraulic press (Shimadzu SSP10A) (20 kg/cm² for 10 seconds).

Dissolution profile

Samples - UC, C8, C10, M8, M10, Asalit® 400 mg and Pentasa® 500 mg - were evaluated on a Hanson® SR6 dissolutor (apparatus 2, 100 rpm, 37 °C ± 0.5 °C) for twelve hours divided into three stages according to the methodology described by Chuong, Christensen and Ayres, 2008. Samples of 10 mL were withdrawn (with replacement) at the times 5, 15, 30, 60, 90, 120, 125, 135, 150, 180, 210, 240, 270, 300, 360, 480 and 720 minutes. The concentration of dissolved drug was measured by spectrophotometer (Shimadzu) UV/VIS - at wavelengths of 302, 330 and 332 nm for the first, second and third stages, respectively.

RESULTS AND DISCUSSION

The average particle size obtained for pellets developed was 0.9977 mm, which is consistent with the extruder diameter (1 mm).

The evaluation of friability (0.95%) showed that the pellets have a high mechanical strength. This is due to the extrusion process that promoted mass compaction, producing dense and less friable extruded mass, which after spheronization was made into pellets with low friability, able to withstand the polymer coating process to modify the release of mesalazine (O'Connor, Schwartz, 1989).

The parameter sphericity shape factor e_R was established by Podczek and Newton (1994, 1995), where the value of unity is considered a perfect sphere, although values greater than 0.6 characterize a particle of good sphericity. The value of e_R determined for the pellets was 0.49 for UC, 0.50 for C8 and 0.53 for C10. There was a gradual increase in the value of e_R accompanied by a reduction of the ratio between the radii, evidencing an improvement in the sphericity of the pellets after coating.

Table I contains the results (n = 3) determined for mesalazine content in a sample of 100 mg of UC, C8 and C10. The content of UC is in agreement with this formulation and serves as a reference for determining the level of coating of C8 and C10. As expected, a reduction in the content of mesalazine in the coated lots was observed, proportionate to the level of coating applied.

The values for the coating level (mg%) found for the two developed products were in accordance with the planned weight gain (8% and 10% application of film coating) calculated based on the mesalazine content in the pellets without coating.

TABLE I - Content of mesalazine in UC, C8, C10 And Coating Level of C8 And C10

	Content of mesalazine (mg%)	Coating level (mg%)	Coating level (mg%)
UC	35.713± 0.04	-	
C8	33.467± 0.06	2.246	6.30
C10	32.380± 0.21	3.333	9.48

The dissolution profile of the reference product Asalit® 400 mg was shown to be pH dependent, consistent with colonic-release drugs. The release of mesalazine from the Asalit® tablets is regulated by a reservoir system. After the dissolution of the coating, the release is very fast. The typical sigmoid shape of the curve indicates that the disintegration and dissolution are of comparable levels. The behavior at different pH values corresponds with the expectations: fast release at pH 7.2 and no release at pH 6.0 and pH 1.0 (Stolk *et al*, 1990) (Figure 1).

For Pentasa® tablets, the release occurs by the principle of dissolution by diffusion from microgranules

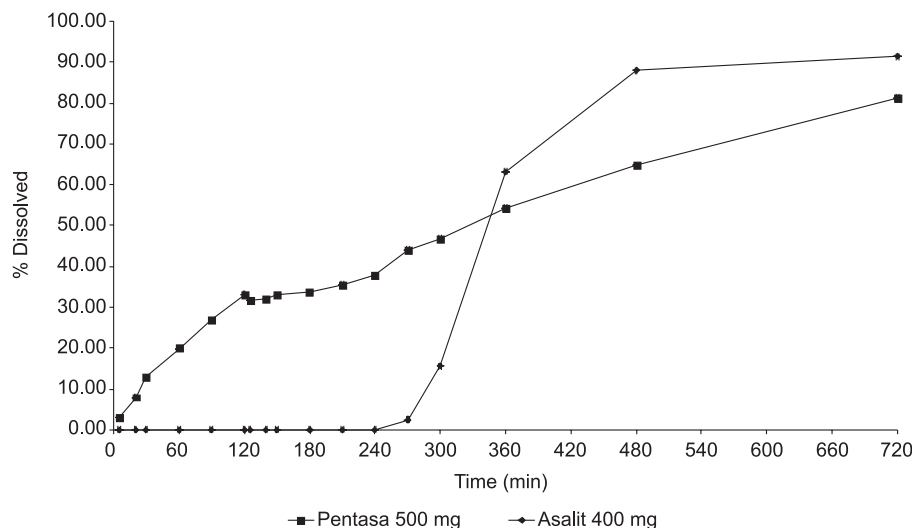


FIGURE 1 - Dissolution profile of reference products Asalit® and Pentasa®.

coated with ethylcellulose (Stolk *et al.*, 1990). Pentasa® tablets in contact with the dissolution medium disintegrate into ethylcellulose-coated granules. The erosion in the ethylcellulose coating is not dependent on pH, therefore the highest levels of drug release in the stomach are best explained by the release controlled by diffusion. The 5-ASA in the external parts of the granules dissolves rapidly in acidic medium. Subsequently, the levels of release decrease gradually due to the time needed for the internal 5-ASA to diffuse to the surface (Schellekens *et al.*, 2007). Similar data were obtained on a different system *in vitro*, by Stolk *et al.* (1990).

The uncoated pellets were dissolved in simulated gastric fluid, attaining over 90% release in 120 minutes of testing, behaving as an immediate release dosage form. This behavior was expected, because there is no excipient in the composition with features that modify drug release.

The coated pellets (8 to 10%) and Asalit® 400 mg showed pH dependent dissolution profiles. For Asalit®, dissolution of the drug began only after 240 minutes of testing, when a change in pH to 7.2 occurred, with release reaching over 90% after 720 minutes of testing. This behavior was expected given this constitutes a monolithic tablet coated with a gastro-resistant methacrylic-derived polymer (Eudragit® S) which dissolves only at pH > 7.0 (Chuong, Christensen, Ayres, 2008).

For coated pellets (8% to 10%), a slight dissolution was seen at pHs below 7.2 (less than 1%), whereas significant dissolution began only after 240 minutes of testing. This shows that the polymer used in the coating provided good control over drug release for both coating levels evaluated (8% and 10%), with little noticeable difference between them. The 10% coated pellets 10% however, de-

monstrated slightly higher retention of the drug, as a result of the higher amount of polymer used, and consequently their dissolution profile more closely resembled that of Asalit® (Figure 2).

In contrast to dissolution of coated pellets (8% and 10%), where there is controlled release promoted by the coating, and significant drug release only at pH 7.2, in multiparticulate tablets from coated pellets (8% and 10%) the compressive force applied was found to have damaged the coating, facilitating the disintegration of the pellets and the release of the drug into the dissolution medium.

As a result of this effect, the release of the drug in these damaged pellets began rapidly in acidic medium, presenting behavior of immediate release, in which drug release occurs in the first few minutes of testing. It is also assumed that some pellets remained intact inside the tablet, and after being released from the dosage form behaved similarly to the coated pellets. Drug release was thus perpetuated until the end of the test, generating a release profile which resembled an extended release form (Figure 3).

In Figure 3, the low dissolution of the drug found at the pH level of 6.0 (between 120-240 minutes) can be explained by its proximity to the isoelectric point (pH 4.3), at which its solubility is lower than for other values of pH used (Langenbucher, 1976).

The efficiency of dissolution (ED) was calculated from the dissolved percentage curves *versus* time, after determining the area under the curve (AUC) and the total area of the graph. The results of the efficiency of dissolution in percent (ED%) for Asalit®, Pentasa® and the formulations are shown in Table II.

The ED% assessment entailed statistical analysis (software MSTAT-C, v.2.11) to infer the similarity between

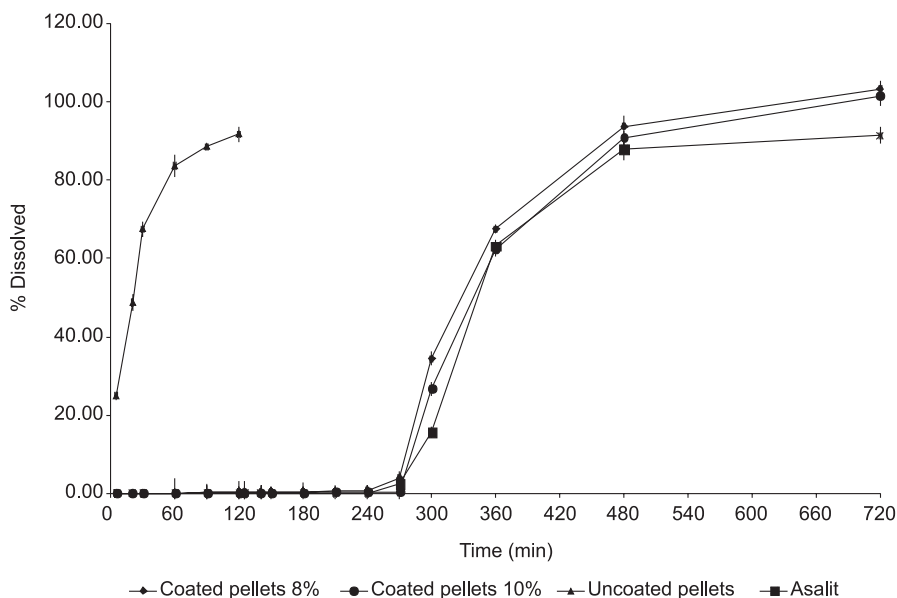


FIGURE 2 - Dissolution profile of pellets (UC, C8, and C10) compared to reference drug Asalit®.

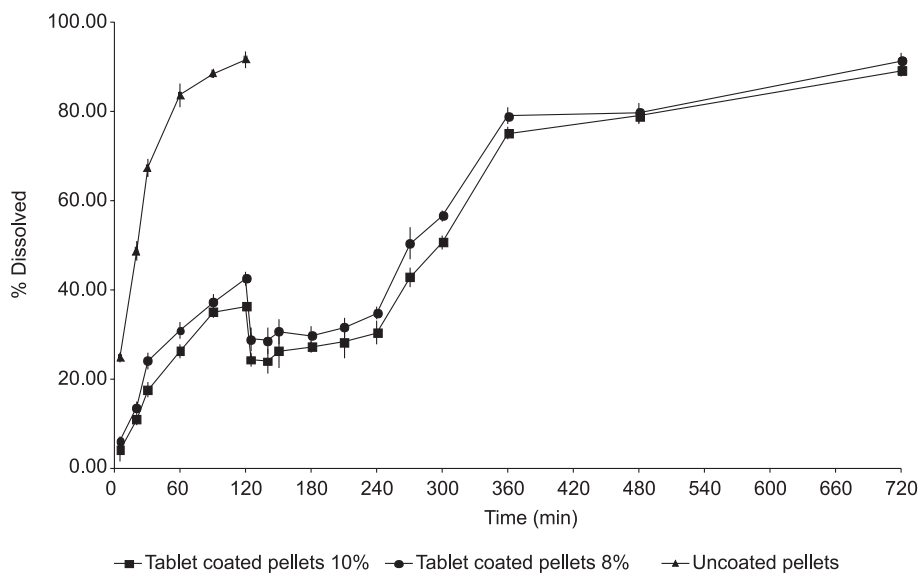


FIGURE 3 - Dissolution profile of multiparticulate systems developed.

TABLE II - Efficiency of dissolution values (%)

Product	ED (%)
Asalit®	45.75 ± 1.74
Pentasa®	50.94 ± 3.42
C8	51.52 ± 1.27
C10	49.22 ± 2.4
M8	60.38 ± 2.57
M10	59.07 ± 2.4

the dissolution profiles studied. Statistical comparison was performed between means, using analysis of va-

riance (ANOVA-single factor), the descriptive level ($P=4.125 \cdot 10^{-5}$) and F value calculated at a significance level of 5% ($F=17.249$; $F_{critical}=3.106$). The homogeneity of variances evaluated by Bartlett's test ($p < 0.01$) showed $\chi^2 = 1.765$ compared with tabulated values of $\chi^2 \alpha (5) = 15.09$, confirming a significant difference between the formulations studied. Therefore, the means of treatments were compared using Tukey's test at 1% probability ($\Delta = 0.08437$) indicating that the difference between the averages were statistically significant.

No statistical difference among mean ED% of Pentasa® 500 mg and Asalit® 400 mg, C8 and C10 was

found, although Asalit® and coated pellets (8% and 10%) both had a pH-dependent dissolution profile. This similarity is probably due to the rapid drug release in these products upon reaching their start time of 270 min (pH 7.2), compensating for the initial release of the drug in acidic medium seen in Pentasa® extending until the end point of the test.

The C10 sample was found to be similar to Asalit® 400 mg, a finding which may be explained by the higher amount of polymer used in this coating, providing better control of drug release.

The multiparticulate tablets showed no similarity with any of the pharmaceutical forms studied, although they exhibited a dissolution profile that resembles extended release forms. This unexpected behavior can be explained by the presence of damaged coated pellets together with intact coated pellets in the dissolution medium.

CONCLUSION

The technique of pelletization by extrusion and spheronization resulted in the obtention of sufficiently spherical and smooth pellets, with a uniform size distribution and adequate mechanical strength to withstand the coating process.

The coating process contributed toward improving the sphericity of the pellets.

The dissolution profile of coated pellets showed good control over drug release from the polymer for both coating levels evaluated (8% and 10%), indicating that the methacrylic derivative used is suitable for achieving modified release systems.

Only coated pellets (10%) had a similar dissolution profile to that of Asalit® 400 mg, according to ANOVA - single factor analysis.

The multiparticulate tablets showed no similarity to any of the pharmaceuticals forms studied, possibly due to rupture of the coating during the compression process.

Mesalazine pellets coated with methacrylic-derived polymer (10%), represents a feasible strategy to achieve therapeutic systems for drug release at the colon, allowing the possibility of producing these systems from hard gelatin capsules.

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