

RESEARCH PAPER

Application of Hydroalcoholic Solutions of Formaldehyde in Preparation of Acetylsalicylic Acid Gastro-resistant Capsules

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ABSTRACT

Enteric coating of hard gelatin capsules by application of hydroalcoholic solutions of formaldehyde was studied and developed in accordance with previous publications. It is possible to affirm that this coating constitutes a simple, stable, reproducible, and inexpensive method, being a valid alternative to those which have been proposed. The aim of the present investigation is the preparation of acetylsalicylic acid gelatin capsules with good conditions of gastro-resistance and enterosolubility.

Key Words: *Acetylsalicylic acid; Disintegration; Drug release; Formaldehyde; Gastro-resistant capsules; Stability*

INTRODUCTION

Acetylsalicylic acid is one of the most useful drugs because of its analgesic, antipyretic, anti-inflammatory, and inhibitory effects on platelet aggregation. However, the use of this drug can cause complications such as gastro-irritation, ulcers, and gastric hemorrhage. These problems can be diminished by an enteric coating that eliminates dissolution in the

stomach, thus protecting the gastric mucosa from the erosive action of acetylsalicylic acid (1,2).

The high enteric absorption of acetylsalicylic acid can seem contradictory if only the pH partition theory is considered (3). Several studies demonstrate that apparently ionized drugs in totality can be absorbed, because a pH value of 5.3 is present at the intestinal epithelium, which defines the dissociation degree of the drug that is absorbed. On the

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other hand it was proved that, when a drug has high permeability through the intestinal mucosa, its absorption rate is related to the circulation rate, which is higher than in the gastric mucosa. These two facts, associated with the greater intestinal surface, explain the high enteric absorption of the acetylsalicylic acid (4,5). Paying attention to previous considerations, it is possible to affirm that this drug must be submitted to an enteric coating.

The basis of the described enteric procedure is the crosslinking of gelatin with formaldehyde. In previous work, this reaction was monitored by Fourier transform-infrared (FT-IR) spectroscopy. Principal component regression analysis of the spectra recorded at different times was carried out in order to ensure that spectral vibration was more objectively analyzed. The results demonstrate that the reaction is initialized by the lysine-methylol formation and is subsequently followed by arginine-methylol, which in turn reacts with lysine-methylol to originate arginine-lysine crosslinks (6).

The main purpose of this study is to obtain stable gastro-resistant acetylsalicylic gelatin capsules, taking into consideration that not more than 10% of the drug should be released from capsules on in vitro dissolution in simulated gastric fluid (2 hr), and that in a subsequent test using simulated intestinal fluid (0.75 hr), not less than 75% of the active ingredient should be dissolved (7,8).

MATERIALS AND METHODS

Materials

The materials employed were as follows: 00, 0 hard gelatin capsules (colorless; Capsugel, Colmar, France), 0 hard gelatin capsules (not transparent; Capsugel). Acetylsalicylic acid (125–315 μm ; 125–400 μm ; Bayer, Coimbra, Portugal). Simulated gastric and intestinal fluids [preparation carried out in accordance with USP XXII (8)]. Ethyl alcohol 75% (v/v), formaldehyde (36.6% w/w), and sodium hydroxide, all of analytical grade (Merck, Lisboa, Portugal).

Formulations

Preliminary tests were carried out to define the acetylsalicylic acid granulometry and the conditions of formaldehyde treatment, which allowed us to obtain the previously established properties.

Relative to the drug release in simulated gastric fluid, the best results were achieved when the capsules were filled with acetylsalicylic acid (125–315 μm) but the drug showed a “clumping effect,” with a low drug release in simulated intestinal fluid; this fact was observed by other researchers (9,10). So, the capsules were filled manually with acetylsalicylic acid (125–400 μm) and sealed in accordance with previous work (11–13).

Coating Procedure

The different capsules were subjected to the following regime:

- formaldehyde concentration 3% (prepared from formaldehyde 36.6% w/w 8.2 g, ethyl alcohol 95% v/v 71.1 g, and water 20.7 g);
- alc. degree of formaldehyde solution 75% (v/v);
- immersion time in formaldehyde solution 15 min;
- first drying at 37°C for 30 min;
- washing with alcohol 75% (v/v) for 15 min;
- second drying at 37°C for 16 hr

or:

- second drying at 37°C for 30 min+15.5 hr at ambient temperature.

Characteristics of the Formulations

The appearance of capsule shells and contents was observed. The weight uniformity was determined in accordance with Farmacopeia Portuguesa V (FPV) (14).

Capsule Size

The studies were carried out with acetylsalicylic acid capsules (00, 665 mg) and (0, 476 mg); the referred amounts allowed their filling up.

Quantification of Free and Residual Formaldehyde

The values of free and residual formaldehyde were respectively determined by high-performance liquid chromatography (HPLC) measurements (12,15).

Quantification of Active Substance

Drug concentrations in simulated gastric and intestinal fluids were determined spectrophotometrically from the formulations at 303 nm (16,17).

Disintegration Testing

The disintegration performance of capsules was evaluated as described previously (12).

Dissolution Testing

The different capsules (attached with a few turns of wire helix that would otherwise float) were subjected to dissolution testing using a dissolution apparatus with rotative paddle (Hanson Research, Northridge, CA, USA) for 2 hr in simulated gastric fluid maintained at 37°C and at speed 50 rpm. After this time the intact capsules were first rinsed in water and immediately immersed in simulated intestinal fluid for 75 min. Filtered samples were withdrawn and analyzed spectrophotometrically, at regular intervals.

Stability Studies

During the storage, the gastro-resistant dosage forms are subjected to physical and chemical alterations than can modify the bioavailability and bioavailability of drugs (18,19). Paying attention to these considerations, residual formaldehyde, disintegration, and dissolution tests were determined on capsules, immediately after coating and at the end of 1, 2, 3, and 6 months of holding the capsules packed in plastic bottles, well stoppered, at 37°C and a relative humidity of 20–25%, or at ambient temperature and a relative humidity of 40–50%.

RESULTS AND DISCUSSION

Characteristics of the Formulations

During our study the capsules presented no physical or content modifications. Weight uniformity was in accordance with the limits of FPV (14).

Determination of “Free” and Residual Formaldehyde

The results from Table 1 demonstrate that higher values are represented by colorless capsules (00), validating the previous results (12). The colorless and not transparent capsules (0) showed identical results, which indicates that the presence of titanium dioxide does not affect the coating procedure.

On the other hand Tables 2 and 3 indicate that the residual formaldehyde changed with the inverse ratio of the ageing time, but from 3 months of storage onwards stabilization is evident. These results are in accordance with a previous study (12). The residual formaldehyde concentration does not constitute any difficulty for capsule administration (20).

Table 1

“Free” Formaldehyde in Washing Alcohol

Batch	“Free” Formaldehyde ^a (mg/capsule)	SD ^b	CV (%)
Colorless 00	0.662±0.041	0.033	4.94
Colorless 0	0.438±0.027	0.022	4.95
Not transparent 0	0.456±0.007	0.005	1.20

^aMean values of five experiments±confidence interval (95%).

^bStandard deviation.

Table 2

Residual Formaldehyde After Second Drying at 37°C

Batch	Residual Formaldehyde ^a (mg/capsule)			
	After Coating	1 Month	3 Months	6 Months
Colorless 00	0.411±0.015	0.102±0.007	0.077±0.007	0.066±0.002
Colorless 0	0.312±0.010	0.078±0.001	0.048±0.005	0.041±0.002
Not transparent 0	0.310±0.020	0.075±0.004	0.041±0.003	0.039±0.004

^aMean values of five experiments±confidence interval (95%).

Disintegration Time of Capsules

The disintegration time of uncoated capsules was 2 min in simulated gastric fluid. Tables 4 and 5 show that the disintegration performance was constant during storage for all capsules.

Dissolution Testing

The results related to the dissolution profiles of the studied formulations are shown in Figs. 1–7. The described results allow us to conclude the following: the studied coating makes it possible to

obtain capsules with a good gastro-resistance, presenting an acetylsalicylic acid release in simulated gastric fluid lower than 5% and in simulated intestinal fluid greater than 85% at the end of 45 min for all kinds of capsules tested. The drying procedure, size, or gelatin composition did not influence the obtained results.

Stability Studies

Analyzing the identical results of residual formaldehyde, disintegration, and dissolution times for all tested capsules after 1, 3, and 6 months of storage,

Table 3

Residual Formaldehyde After Second Drying at Ambient Temperature

Batch	Residual Formaldehyde ^a (mg/capsule)			
	After Coating	1 Month	3 Months	6 Months
Colorless 00	0.428±0.007	0.108±0.007	0.087±0.003	0.080±0.004
Colorless 0	0.335±0.012	0.083±0.003	0.047±0.002	0.042±0.004
Not transparent 0	0.336±0.008	0.065±0.004	0.045±0.004	0.039±0.003

^aMean values from five experiments±confidence interval (95%).

Table 4

Disintegration Time in Simulated Intestinal Fluid for Dried Capsules at 37°C

Batch	Disintegration Time ^a (min)			
	After Coating	1 Month	3 Months	6 Months
Colorless 00	9.1±0.7	8.5±0.6	8.4±0.5	8.4±0.5
Colorless 0	8.5±0.6	8.7±0.6	8.7±0.3	8.8±0.3
Not transparent 0	8.9±0.3	8.3±0.6	8.4±0.5	8.6±0.5

^aMean values from five experiments±confidence interval (95%).

Table 5

Disintegration Time in Simulated Intestinal Fluid for Dried Capsules at Ambient Temperature

Batch	Disintegration Time ^a (min)			
	After Coating	1 Month	3 Months	6 Months
Colorless 00	8.7±0.3	8.8±0.9	9.0±1.0	9.0±0.8
Colorless 0	8.7±0.6	8.3±0.7	8.4±0.5	8.9±0.8
Not transparent 0	8.6±0.5	8.6±0.5	8.8±0.3	8.6±0.5

^aMean values from five experiments±confidence interval (95%).

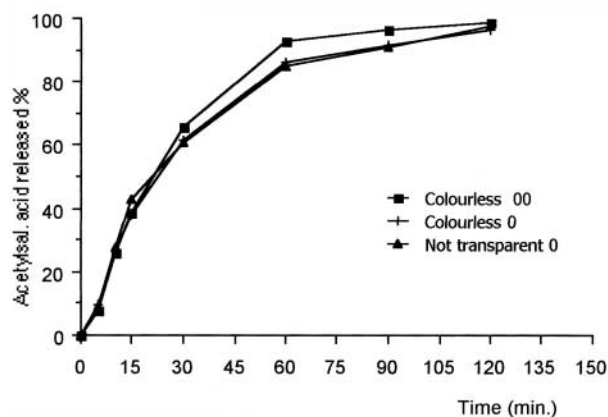


Figure 1. Dissolution profile of uncoated capsules.

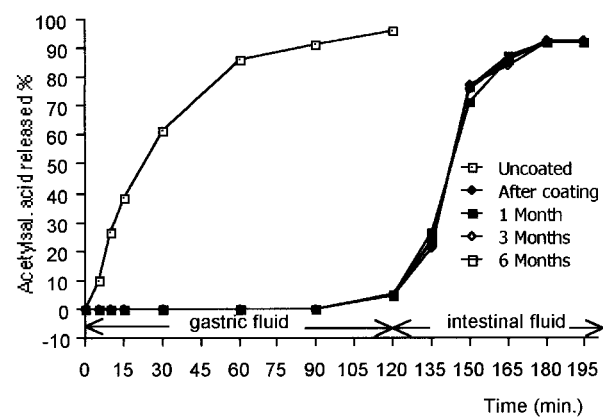


Figure 4. Dissolution profile of dried colorless 0 capsules at 37°C

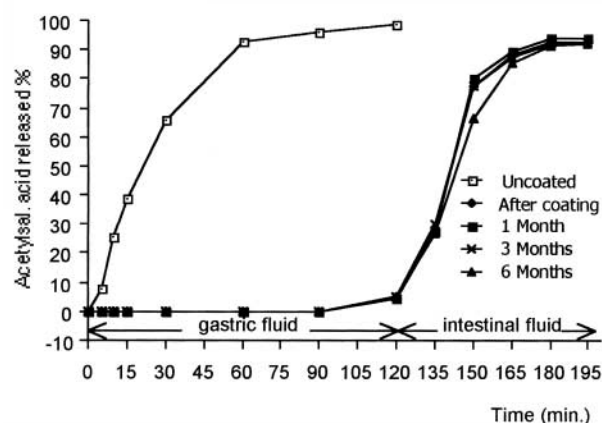


Figure 2. Dissolution profile of dried 00 capsules at 37°C.

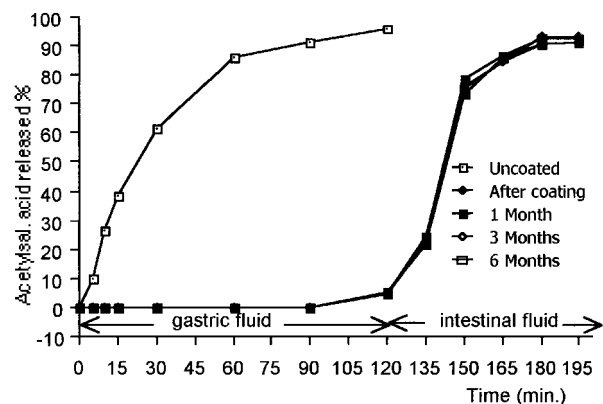


Figure 5. Dissolution profile of dried colorless 0 capsules at ambient temperature.

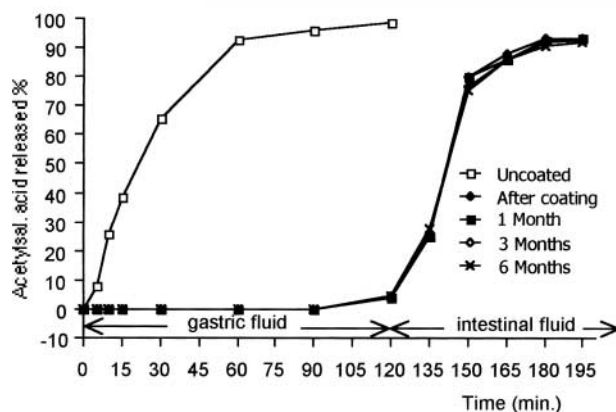


Figure 3. Dissolution profile of dried 00 capsules at ambient temperature.

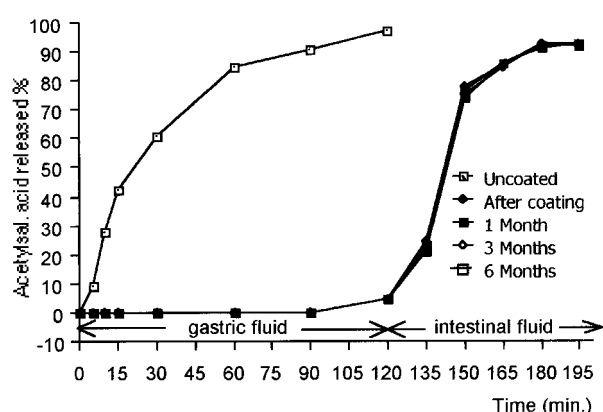


Figure 6. Dissolution profile of dried not transparent 0 capsules at 37°C.

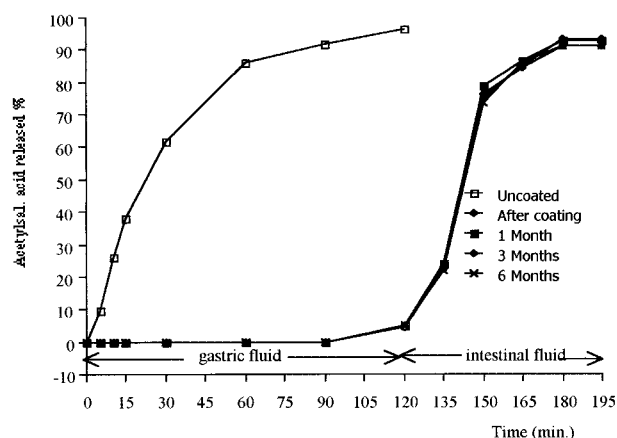


Figure 7. Dissolution profile of dried not transparent 0 capsules at ambient temperature.

at 37°C and at ambient temperature, we verify a stabilization of the coating procedure.

CONCLUSIONS

The studied coating allowed us to obtain stable acetylsalicylic acid gelatin capsules with a good gastro-resistance and enterosolubility, in accordance with the proposed objectives.

The properties of prepared gelatin capsules are identical to those obtained by other researchers, although using a different experimental methodology (21,22).

From these results it is possible to affirm that the application of formaldehyde constitutes a valid alternative to those methods developed for the enteric coating of acetylsalicylic acid gelatin capsules.

ACKNOWLEDGMENT

The authors acknowledge the financial support of the Centro de Estudos Farmacêuticos, Faculty of Pharmacy, University of Coimbra.

REFERENCES

1. Anslow, J.A.; Greene, D.S. Faster and More Reliable Delivery of Salicylic Acid from Enteric-Coated Aspirin Granules Versus Enteric-Coated Aspirin Tablets. *Curr. Ther. Res.* **1984**, *36* (5), 811–818.
2. Nikolic, L.; Zorica, D.; Jovanovic, M. Influence of In Vitro Test Conditions on Release of Aspirin from Commercial Tablets. *J. Pharm. Sci.* **1992**, *81* (4), 386–391.
3. Buri, P. Préformulation: pK_a et Coefficient de Partage. *Labo-Pharma. Probl. Téchn.* **1981**, *307* (3), 181–186.
4. Delporte, J.P.; Jaminet, F. Influence de la Formulation des Préparations Entérosolubles sur la Disponibilité Physiologique du Principe Actif. 4^a Partie: Influence du pH de Dissolution du Polymère D'Enrobage Appliqué sur des Comprimés d'Acide Acétylsalicylique sur leurs Caractéristiques d'Absorption "In Vivo". *Conclusions. J. Pharm. Belg.* **1976**, *31* (3), 263–276.
5. Morais, J.G. O Medicamento e o seu Comportamento no Organismo. Liberação, Absorção, Distribuição e Excreção (LADME). *Farmacocinética. Farm. Port.* **1984**, *27* (3/4), 13–24.
6. Salsa, T.; Pina, M.E.; Teixeira-Dias, J.J.C. Crosslinking of Gelatin in the Reaction with Formaldehyde: an FT-IR Spectroscopic Study. *Appl. Spectrosc.* **1996**, *50* (10), 1314–1318.
7. Möller, H.; Wirbitzki, E. Special Cases of Dissolution Testing Using the Flow Through System. *STP Pharma* **1990**, *6* (9), 657–662.
8. *U.S. Pharmacopeia XXII*, U.S. Pharmacopeial Convention, Rockville, MD, 1990.
9. Newton, J.M.; Bader, F. The Influence of Drug and Diluent Particle Size on the In Vitro Release of Drug from Hard Gelatin Capsules. *J. Pharm. Pharmacol.* **1980**, *32*, 167–171.
10. Niskanen, M. Explaining the Dissolution Properties of Theophylline Pellets by Their Microstructure. *Pharm. Technol. Int.* **1992**, *9*, 20–28.
11. Pina, M.E. Gastro-Resistência Estabilidade e Bio-disponibilidade de Cápsulas Gelatinosas Formiladas. Ph.D. Thesis, Faculdade de Farmácia, Coimbra, 1994; 189 pp.
12. Pina, M.E.; Sousa, A.T.; Brojo, A.P. Enteric Coating of Hard Gelatin Capsules. Part 1. Application of Hydroalcoholic Solutions of Formaldehyde in Preparation of Gastro-resistant Capsules. *Int. J. Pharm.* **1996**, *133*, 139–148.
13. Pina, M.E.; Sousa, A.T.; Brojo, A.P. Enteric Coating of Hard Gelatin Capsules. Part 2. Bioavailability of Formaldehyde Treated Capsules. *Int. J. Pharm.* **1997**, *148*, 73–84.
14. *Farmacopeia Portuguesa V*, Edição Oficial, Parte 1, Imprensa Nacional-Casa da Moeda, Lisboa, 1986.
15. Pina, E.; Sousa, A.T.; Brojo, A.P. HPLC Method Development and Validation for Formaldehyde in Enteric Coating of Hard Gelatin Capsules. *J. Liq. Chromatogr.* **1995**, *18* (13), 2683–2693.
16. Embil, K.; Torosian, G. Dissolution Behaviour of Commercial Enteric Coated Aspirin Tablets. *J. Pharm. Sci.* **1979**, *68* (10), 1290–1292.

17. Plaizier-Vercammen, J.P.; Suenens, G. Evaluation of Aquateric, a Pseudolatex of Cellulose Acetate Phthalate, for Its Enteric Coating Properties on Tablets. *STP Pharma Sci.* **1991**, *1* (5), 307–312.
18. Thoma, K. La Disponibilité Pharmaceutique Comme Critère Essentiel de Qualité. *STP Pharma* **1987**, *1* (hors-série), 39–50.
19. Murthy, K.S.; Ghebre-Sellassie, I. Current Perspectives on the Dissolution Stability of Solid Oral Dosage Forms. *J. Pharm. Sci.* **1993**, *82* (2), 113–126.
20. World Health Organization. *Formaldehyde*; WHO: Geneva, 1989; 13.
21. Plaizier-Vercammen, J.P.; Van Molle, V.M.V. Evaluation of Aqueous Dispersions of Eudragit L 100-55 for Their Enteric Coating Properties *STP Pharma Sci.* **1991**, *1* (4), 267–271.
22. Cherretté, I.; Plaizier-Vercammen, J.A. Evaluation of a Water Dispersion of Aquateric for Its Enteric Coating Properties of Hard Gelatin Capsules Manufactured with a Fluidized Bed Technique. *Pharm. Acta Helv.* **1992**, *67* (8), 227–230.

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