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Enteric coating of hard gelatin capsules. Part 1. Application of hydroalcoholic solutions of formaldehyde in preparation of gastro-resistant capsules

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Abstract

A evaluation of coating methods currently in use leads to the conclusion that the application of gastro-resistant coatings which remain stable over the shelf life of hard capsules is extremely difficult due to the inherent characteristics of the gelatinous shells. The main purpose of this study was to develop a simple, stable and reproducible method, based on crosslinking gelatin with formaldehyde, which could constitute a valid alternative to those which have been proposed.

Keywords: Capsules; Enteric coating; Formaldehyde; Disintegration; Stability

1. Introduction

Gastrointestinal tract resistant capsules are commonly used for several purposes. Among these are the protection of the active substance from being destroyed by the gastric contents — either enzymes or highly acidic gastric fluids; prevention or reduction of nausea and vomiting associated with a drug's irritation; delivery of the drug to its absorption site in the intestine; production of microbial or enzymatic preparations (the technological operations are less complex and traumatic than those required for tablet production). They also provide useful information on the pharmacological efficacy and pharmacokinetics of new substances that are unstable in or irritating to the gastric mucosa, avoiding the problems involved in preparation of enteric coated pellets or tablets and eliminating the need for extensive efforts in formula development (Delporte, 1970; Gumma and Mirimanoff, 1971; Aiache et al., 1975; Cier et al., 1979; Murthy et al., 1986; Hannula and Speiser, 1988; Prista et al., 1991).

The evaluation of different coating methods for capsules proved it to be especially difficult to put gastro-resistant and stable coatings into use due to the smooth, non-porous and non-absorptive nature of the shell materials. The aim of this work is to establish a process of easy application that can be considered a valid alternative to presently proposed methods.

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A review of the literature concerning the employment of formaldehyde in enteric coating of capsules demonstrates that the most important parameters in formaldehyde–gelatin crosslinking are: the formaldehyde concentration and contact time with formaldehyde, temperature, relative humidity and storage time (Brojo and Sousa, 1972; Cognyl, 1974).

On the other hand, in relation to formaldehyde–gelatin crosslinking, there is evidence that residual formaldehyde, capable of promoting a higher hardening of gelatin shells, may remain behind after capsule coating. This would compromise enteric disintegration and explain the majority of failures when testing this coating process (Pina, 1994).

The present study is divided in two main parts. In the first part the influence of different parameters on the gastro-resistance of the formaldehyde treated capsules is evaluated along with the quantification of formaldehyde in different phases and under different process conditions. Finally, the conditions which allow the entero-solubility stabilization of the capsules are defined.

In the second part, to be published in the near future, the dissolution profiles of the formaldehyde treated capsules with different contents, which lead to different release models, are presented. These investigations made it possible to evaluate the quality, potentialities and limitations of the developed coating process. The choice of content considered different solubilities as this is one of the most important parameters affecting the release rate from capsules.

2. Materials and methods

2.1. Materials

The materials employed were as follows: 00 hard gelatin capsules (colourless, Capsugel), lactose, powdered gelatin and ethyl alcohol 95% (v/v), formaldehyde (36.6% w/w), absolute ethanol, pepsin (70 FIP-U/g), sodium chloride, hydrochloric acid, pancreatin (350 FIP-U/g protease, 7500 FIP-U/g lipase, 7500 FIP-U/g amylase), monobasic potassium phosphate, sodium hydroxide, all analytical grades (Merck).

2.2. Preparation of capsules

Capsules were filled with 100% lactose and sealed by banding with an aqueous solution of gelatin (10%) (Brojo and Sousa, 1972; Cole, 1987; Pina et al., 1987, Scott et al., 1992).

2.3. Coating solutions

Several formaldehyde solutions (1–5%) with different alcohol contents (20–99%, v/v) were prepared.

Table 1
Effect of formaldehyde concentration and alcoholic content on its solution

Batches	Disintegration time (min)[a]	
	Gastric juice	Enteric juice
L–1/90	115 (8)	5
L–1/95	100	—
L–1/99	48	—
L–2/80	90 (6)	4
L–2/85	75 (7)	4
L–2/90	—	4
L–2/95	10 (6)	2
L–2/99	74	—
L–3/75	—	>60
L–3/80	—	>60
L–3/85	—	45 (6)
		>60 (6)
L–3/90	—	20 (4)
		>60 (8)
L–3/95	67 (6)	5
L–4/70	—	>60
L–4/75	—	>60
L–4/80	—	>60
L–4/85	—	>60
L–4/90	—	40 (2)
		>60 (10)
L–5/60	—	>60
L–5/70	—	>60
L–5/75	—	>60
L–5/80	—	>60
L–5/85	—	>60
L–5/90	—	>60

[a]The results between parentheses refer to the number of capsules in each batch which disintegrate at the times shown.

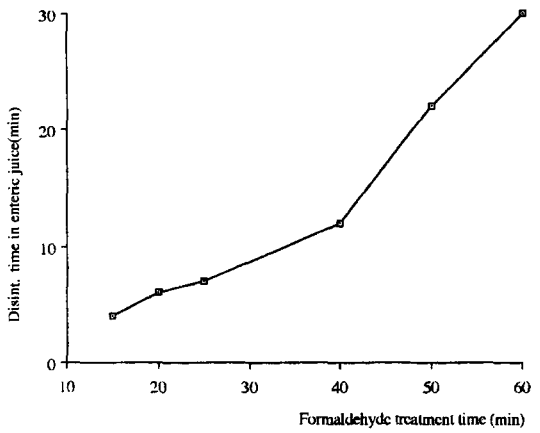

Fig. 1. Effect of time formaldehyde treatment on disintegration (L–2/90).

2.4. Coating procedure

Each batch, consisting of 12 units, was coated by immersion (with stirring) in a clean vial well stoppered, containing 100 g of each test solution for 15 min at ambient temperature.

2.5. Drying procedure

Capsules were dried in an oven, at 37°C for 30 min. The coated capsules were then dried for 24 h, at ambient temperature prior to testing.

2.6. Disintegration test

Twelve capsules were exposed for 2 h at 37°C to gastric juice (US Pharmacopeia XXII, 1990) using a disintegration apparatus (Erweka, ZT3-2). After this time, the intact capsules were first rinsed with water and immediately immersed in enteric juice (US Pharmacopeia XXII, 1990).

2.7. Parameters affecting gastro-resistance of formaldehyde treated capsules

2.7.1. Formaldehyde concentration and alcohol content of its solution

Lactose capsules were treated with coatings solutions, previously described and subjected to the disintegration test.

2.7.2. Immersion time in formaldehyde solution

Lactose capsules were treated with the formaldehyde solution (2%, 90% v/v) for different times from 15 to 60 min.

2.7.3. Drying and alcohol 'washing' subsequent to formaldehyde treatment

Lactose capsules (00; 838 mg) were subjected to the following regime: (1) Formaldehyde treatment: formaldehyde concentrations, 1.5 and 2%; alcohol content of the formaldehyde solution, 90% (v/v); immersion time in formaldehyde solution, 15 min. (2) Drying at 37°C for 30 or 60 min, plus 24 h at ambient temperature (batches I–IV), or, first drying at 37°C for 30 min plus washing in 95% (v/v) alcohol for 30 min plus a second drying at 37°C for 30 min plus 24 h at ambient temperature (batches V and VI).

For alcohol 'washing', the capsules were stirred in a stoppered vial, with alcohol (10 ml/caps) at ambient temperature.

2.7.4. Composition of capsules

The compositions of the three capsule types were as follows: sucrose capsules, (00; 942 mg) S–2/90; lactose capsules, (00; 838 mg) L–2/90; and talc capsules, (00; 1089 mg) T–2/90.

Formaldehyde treatment was as follows: formaldehyde concentration, 2%; alcohol content of the formaldehyde solution, 90% (v/v); immersion time in formaldehyde solution, 15 min. The drying regime used was 37°C for 30 min, followed by 24 h at ambient temperature.

2.8. Determination of free and residual formaldehyde

2.8.1. Formaldehyde concentration of coating solution

For the talc capsules (00; 1089 mg), the formaldehyde treatment involved formaldehyde concentrations of 2 and 3%, an alcohol content of the formaldehyde solution of 90% (v/v), immersion in the solution for 15 min, followed by drying at 37°C for 30 min.

2.8.1.1. Quantification of 'free' formaldehyde. Subsequent to drying, a batch of capsules was

Table 2
Effect of drying and alcoholic washing after formaldehyde treatment

Batches	Disintegration time (min)[a]	
	Gastric juice	Enteric juice
I: L–1,5/90 — drying/30 + ambient temp.	90 (6)	4
II: L–1,5/90 — drying/60 + ambient temp.	100 (2)	14
III: L–2/90 — drying/30 + ambient temp.	(Little)	4
IV: L–2/90 — s/60 + ambient temp.	—	15
V: L–1,5/90 — drying/30 + washing/30 + drying/30 + ambient temp.	69	—
VI: L–9/90 — drying/30 + washing/30 + drying/30 + ambient temp.	100(2) (None)	2

[a]The results between parenthesis refer to the number of capsules in each batch which disintegrated at the times shown.

'washed' in alcohol (90%, v/v) for 30 min under conditions described in section 2.7.3. One millilitre was withdrawn and used for formaldehyde dosage by HPLC measurement (Pina, 1994, Pina et al., 1995).

2.8.1.2. Quantification of residual formaldehyde. After optimization, the following method was established: two formaldehyde treated capsules were placed in a clean well stoppered vial, containing 20 ml of distilled water. The vial was stirred on a mechanical agitation apparatus for 2 h (Pina, 1994). Subsequently, 1 ml was used for the analysis of residual formaldehyde content by the method referred to previously (Pina, 1994, Pina et al., 1995).

2.8.2. 'Washing' time

The formaldehyde treatment for talc capsules (00; 1089 mg) used a formaldehyde concentration of 2%, an alcohol content of 90% (v/v), an immersion time in the solution of 15 min. This was followed by a first drying at 37°C for 30 min, washing with 90% (v/v) alcohol for 10 and 15 min and a second drying at 37°C for 30 min.

Table 3
Effect of capsules content

Batches	Disintegration time (min)	
	Gastric juice	Enteric juice
S–2/90	100 (None)	—
L–2/90	— (Little)	4
T–2/90	— (Full)	5

2.8.3. Alcohol content of 'washing' alcohol

For the talc capsules (00; 1089 mg) the formaldehyde treatment involved a formaldehyde concentration of 3%, an alcohol content of 75% (v/v). This was followed by drying at 37°C for 30 min and washing with 75% and 95% (v/v) alcohol for 30 min.

2.8.4. Composition of capsules

Compositions were as follows: talc capsules (00, 1089 mg), sucrose capsules (00; 942 mg), and lactose capsules (00; 838 mg). Formaldehyde treatment employed a formaldehyde concentration of 3%, an alcohol content of 75% (v/v), and a 15-min immersion time. This was followed by a first drying at 37°C for 30 min, washing with 75% (v/v) alcohol for 30 min and second drying at 37°C for 16 h.

2.8.5. Capsule size

Talc capsules: 00, 1089 mg and 0, 780 mg. Sucrose capsules: 00, 942 mg and 0, 674, 3 mg. Lactose capsules: 00, 838 mg and 0, 600 mg. Their subsequent treatment as stated in section 2.8.4.

2.8.6. Drying time

For determination of 'free' formaldehyde in talc capsules (00; 1089 mg), the following formaldehyde treatment was used: formaldehyde concentration, 2%; alcohol content of solution, 90% (v/v); immersion time in formaldehyde solution, 15 min.

Drying was at 37°C for 30, 60, 90, and 1440 min, followed by washing with 90% (v/v) alcohol

Table 4
Effect of formaldehyde concentration on coating solution

Coating solution concentration (%)	Free formaldehyde (mg/caps)	Residual formaldehyde (mg/caps)
2	0.436 ± 0.010	0.577 ± 0.072
3	0.516 ± 0.025	0.645 ± 0.020

Table 5
Effect of washing time

Batch	Free formaldehyde (mg/caps)	Residual formaldehyde (mg/caps)
Washing, 10 min	0.302 ± 0.021	
Washing, 10 min + second drying		0.206 ± 0.019
Washing, 15 min	0.393 ± 0.015	
Washing, 15 min + second drying		0.182 ± 0.007

Table 6
Effect of alcohol content of washing alcohol

Alcohol content (% (v/v))	Free formaldehyde (mg/caps)	S	C.V. (%)
75	0.867 ± 0.026	0.021	2.433
95	0.284 ± 0.008	0.007	2.295

for 5 min, or, drying at 37°C for 24 h and 72 h, followed by washing with 90% (v/v) alcohol for 30 min.

For the determination of residual formaldehyde in talc capsules (00; 1089 mg) the formaldehyde treatment was: formaldehyde concentration, 2%; alcohol content, 90% (v/v); immersion time, 15 min. Drying was at 37°C for 30 min (time 0), 24 h, 1 week, 2 weeks, 1 month, and 4 months.

2.9. Stabilization of formaldehyde treated capsules

2.9.1. Effect of first drying, number of washings and second drying conditions

Lactose capsules (00; 838 mg) were subjected to the following formaldehyde treatment: formaldehyde concentration, 5%; alcohol content of solution, 65% (v/v); immersion time, 15 min.

The first drying was accomplished at 37°C for 30 min in five batches and at ambient temperature in a sixth batch; the number of washings in alcohol (95%, v/v) for 30 min changed between one and four and second drying alternated between 30 min and 2 h, all batches were stored at ambient temperature in stoppered vials and submitted to the disintegration test after 24 h, 1, 2 and 3 months.

2.9.2. Effect of second drying time on stabilization of formaldehyde treatment

For lactose capsules (00; 838 mg) the formaldehyde treatment was: formaldehyde concentration, 5%; alcohol content, 65% (v/v); immersion time, 15 min. The first drying was at 37°C for 30 min, followed by washing in 95% (v/v) alcohol for 30 min and a second drying at 37°C for 30 min, 1, 2, 6, 12, 18 and 24 h.

2.9.3. Stabilization of process

Residual formaldehyde and disintegration tests were performed on lactose capsules coated under

Table 7
Effect of capsule composition

Batch	Free formaldehyde (mg/caps)	Residual formaldehyde (mg/caps)
Talc	0.956 ± 0.052	0.376 ± 0.014
Sucrose	0.878 ± 0.042	0.393 ± 0.015
Lactose	1.006 ± 0.067	0.387 ± 0.018

Table 8
Effect of size capsules

Batches	Free formaldehyde (mg/caps)	Residual formaldehyde (mg/caps)
T–00	0.956 ± 0.052	0.376 ± 0.014
T–0	0.467 ± 0.015	0.267 ± 0.015
S–00	0.878 ± 0.042	0.393 ± 0.015
S–0	0.480 ± 0.029	0.244 ± 0.012
L–00	1.006 ± 0.067	0.387 ± 0.018
L–0	0.483 ± 0.015	0.243 ± 0.012

the conditions described in section 2.9.2 (second drying was effected at 37°C, for 16 h) immediately after coating and after 1, 2, 3 and 6 months of holding the capsules packed in plastic bottles, well stoppered, at ambient temperature, and a relative humidity of 45–50%.

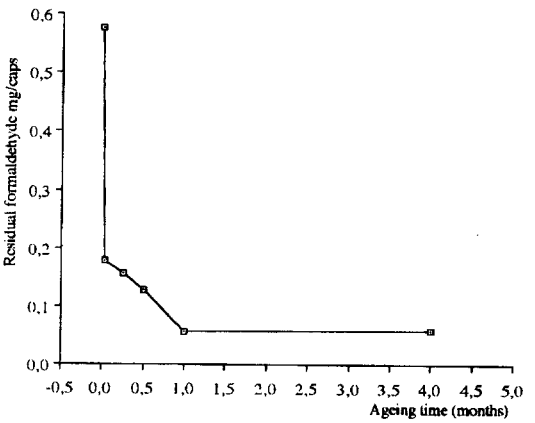

Fig. 2. Effect of ageing time on residual formaldehyde concentration.

3. Results and discussion

3.1. Parameters affecting gastro-resistance of formaldehyde treated capsules

Concerning the influence of formaldehyde concentration and alcohol content of the solution the results are given in Table 1 and indicate the following: The higher the formaldehyde concentration, the lower the alcoholic content necessary for conditions adequate for capsules. Also, an increase of formaldehyde concentration (for the same alcohol content) promotes a higher resistance time to enteric juice (Fraenkel-Conrat et al., 1945; Davis and Tabor, 1963; Brojo and Sousa,

Table 9
Effect of drying on 5 min washing

Drying time (min)	Free formaldehyde (mg/caps)	S	C.V.(%)
30	0.190 ± 0.020	0.016	5.300
60	0.118 ± 0.007	0.006	5.018
90	0.096 ± 0.007	0.005	5.658
1440	0.038 ± 0.003	0.003	5.675

Table 10
Effect of drying on 30 min washing

Drying time hours	Free formaldehyde (mg/caps)	S	C.V.(%)
24	0.087 ± 0.008	0.005	5.868
72	0.037 ± 0.002	0.002	5.212

Table 11
Effect of first drying, number of washings and second drying conditions

Batches	First drying	Number of alc. washing	Second drying (min)	Disintegration time (min)				Increase of disintegration time (%)
				24 h	1 month	2 months	3 months	
L–1	37°C/30 min	1	30	12	31	48	61	408
L–2	37°C/30 min	1	60	17	37	56	64	276
L–3	37°C/30 min	1	20	22	46	65	70	218
L–4	37°C/30 min	3	30	8	18	26	31	288
L–5	37°C/30 min	4	30	6	12	16	18	200
L–6	Ambient	—	—	32	90	138	179	459

1972; El-Said et al., 1987; Gürkan et al., 1987; Dybek et al., 1992); for the lowest formaldehyde concentrations (1, 2 and 3%), the gastro-resistance of capsules is lower when the alcohol content increases (Albert et al., 1989).

As shown in Fig. 1, the disintegration rate of capsules in enteric juice is inversely proportional to their immersion time in formaldehyde solution (Nixon et al., 1968; Brojo and Sousa, 1972, Madan et al., 1976; Gürkan et al., 1987; Chiao and Price, 1989).

The results presented in Table 2 show that when drying time is longer, there is an increase in the disintegration time of capsules (Fraenkel-Conrat et al., 1945; Brojo and Sousa, 1972; Moll et al., 1974); the 'washing' process therefore promotes a decrease in the disintegration time of capsules.

Table 3 demonstrates the effect on disintegration times of capsule content for sucrose, lactose and talc capsules, when treated under similar conditions of formaldehyde concentration and alcohol content. This fact is in accordance with Newton and Razzo (1974), Lerk et al. (1977), Newton and Razzo (1977a,7b), Lerk et al. (1978), Rowley et al. (1985a,b) and Anno and Rees (1985) who packed substances of several solubilities and obtained differences in disintegration and dissolution characteristics of the capsules.

3.2. Determination of 'free' and residual formaldehyde

Results in Table 4 indicate that an increase in the formaldehyde concentration of the coating

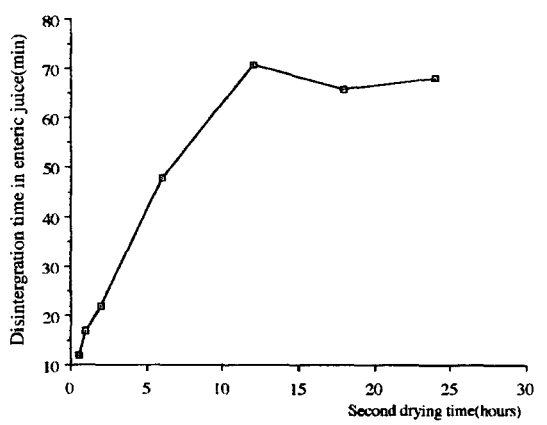

Fig. 3. Effect of second drying.

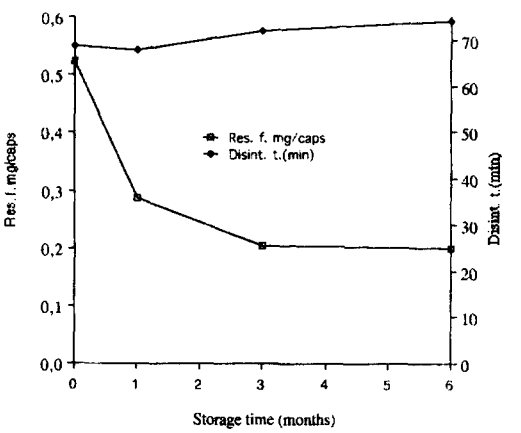

Fig. 4. Stabilization of formaldehyde treatment (L–5/65).

solution promotes higher levels of 'free' and residual formaldehyde. Table 5 shows that during 'washing', 'free' formaldehyde is extracted and its concentration increases when the 'washing' time is longer. On the other hand, residual formaldehyde decreases under these conditions. The results presented in Table 6 reveal different formaldehyde values, which can explained by the fact that 75% (v/v) alcohol extracts more 'free' formaldehyde from gelatin capsules, because of its higher polarity and dielectric constant than 95% (v/v) alcohol (Prista et al., 1991).

The composition of capsules does not influence 'free' and residual formaldehyde concentrations (Table 7). In conjunction with the results obtained with 00 capsules and 0 capsules (Table 8), this verifies that the latter have lower 'free' and residual formaldehyde concentrations, due to their smaller surface area which fixes lower amounts of formaldehyde. Analyzing the results (Table 9 and Table 10), it is possible to prove that 'free' formaldehyde in the 'washing' solution decreased as drying time increased. Residual formaldehyde concentration changed inversely with the length of oven 'ageing', with a higher decrease during first 24 h of drying and stabilization of results after 1 month (Fig. 2). This is in accordance with previous results obtained by Jain and Naik (1984), Annapurna and Subba Rao (1987), Pina et al. (1987) and Pina et al. (1991).

3.3. Stabilization of formaldehyde treated capsules

For the influence of first drying, the number of washings and second drying conditions, the analysis of enteric disintegration times, demonstrates that in all batches a significant and progressive hardening occurred during 3 months of maintenance, without the hoped for stabilization of formaldehyde treated capsules (Table 11). Comparing the disintegration times after 24 h with those attained at the end of 3 months and determining the respective percentage increase for each batch, it is possible to conclude immediately that higher hardening took place in batch L6. These capsules, after treatment with formaldehyde, were dried at ambient temperature, and were not washed in alcohol (95%, v/v). They also showed the highest disintegration time after the first 24 h. The higher humidity, and excess of formaldehyde, explains the continuation of crosslinking during storage, which is in accordance with the reaction mechanism. On the other hand, when the results obtained with batches L4 and L5 are compared, we can conclude that the number of washings, for the same drying conditions, lead to a better removal of formaldehyde, that explains the lower disintegration times at the beginning and the lower percentage increase exhibited, confirming the importance of the washing process (section 2.8.2). Finally, for the same number of washings (1) and an identical drying method, when the drying time is increased (30, 60 and 120 min), the increase in the disintegration time was accompanied by a lower hardening of capsules during storage. The results show the great importance of the second drying as the way to stabilize the formaldehyde–gelatin reaction. This leads to longer disintegration times, soon after coating, but without a significant increase during storage, which is in according with the results of Boymond et al. (1966). The results presented in Fig. 3 show that the increase in heating caused a progressive hardening of capsules, which reaches its highest level after 12 h and remains constant thereafter. Analyzing the results obtained we can conclude (Fig. 4) that the disintegration time of capsules determined after coating reached identical values after 6 months. Fig. 4 also shows that residual formaldehyde changed inversely with ageing time, but after 1 month of storage, stabilization is evident. However, this is not a result of its reaction with gelatin, because the degree of capsules hardening is constant: the reduction in formaldehyde is a consequence of the vaporization process. In a crosslinked gelatin structure some formaldehyde may exist, that is detected by the process described, in accordance with Taylor et al. (1978).

The investigations described here demonstrate the feasibility of preparing satisfactory enteric capsules using formaldehyde in an alcohol solution. For each formula it is necessary to clearly define the formaldehyde concentration, the alcohol content of its solution, the drying and washing processes after treatment with formaldehyde,

and the drying period all of which are essential to the stabilization of gastro-resistance and enterosolubility of the capsules.

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