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BEAD COATING PROCESS *VIA* AN EXCESS OF CROSSLINKING AGENT

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ABSTRACT

Coated beads were prepared by soaking in sodium alginate solutions spherical matrices (beads) of carboxymethylcellulose crosslinked with aluminum chloride ($AlCl_3$) and loaded with ambroxol hydrochloride as a model drug. The residual amount of the crosslinker induced an interfacial crosslinking reaction of the sodium alginate. Therefore, an insoluble, smooth and uniform in thickness coat was formed around the beads. As the coating time increased, the coat thickness increased untill $AlCl_3$ was present inside the beads. The rate of drug release from the coated beads was slower than that from the uncoated beads and decreased with the increase in coating time. Moreover, a constant rate phase, subsequent a burst period for the samples obtained with the highest coating times, was achieved. The dynamic swelling analysis allowed to exclude the influence of the polymer relaxation on the release process which appeared to be controlled by the alginate coat.

INTRODUCTION

The preparation of coated matrices can involve chemical procedures, such as crosslinking reactions of the matrix surface [1] or of a polymer which coats the matrix surface [2].

In the present study, the latter procedure was used to coat carboxymethylcellulose beads obtained previously by crosslinking sodium carboxymethylcellulose with $AlCl_3$ as crosslinking agent [3]. In this previous work [3], crosslinked carboxymethylcellulose beads loaded with the drug by direct method showed fast release processes owing to the presence of a residual amount of $AlCl_3$. In fact, the

removal of the residual amount of $AlCl_3$ obtained through a loading method by swelling allowed to slow the drug release process, which was found to be controlled by a diffusion-type mechanism.

In this paper, in order to obtain systems providing a constant release rate, we decided to coat the beads loaded by the direct method through an interfacial reaction between the residual amount of $AlCl_3$ and sodium alginate. Aqueous solutions of the sodium salt of alginic acid gel in the presence of many polyvalent cations (as Al^{3+}). The gelation involves the cooperative binding of the metal ions, which is described in terms of an egg-box junction model [4].

Thus, coated beads were obtained combining generally accepted materials with a rather simple tecnology.

The morphological characteristics and the drug release process of the coated beads obtained by changing the coating time were evaluated.

MATERIALS AND METHODS

Materials

Ambroxol hydrochloride (trans-4-[(2-amino-3,5-dibromobenzyl)amino]-cyclo-hexanol hydrochloride) (Profarmaco Nobel, Milan, Italy) (MW 414.4; water solubility 2.4×10^{-2} g/ml) was used as the model drug; high viscosity sodium carboxymethylcellulose (NaCMC; Fluka Chemie, Buchs, Switzerland; viscosity of the 4% w/v solution in water at 25°C 1000-1500 mPa·s; degree of substitution 0.70-0.85), aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$) (Carlo Erba, Milan, Italy) and Tween 20 (polyoxyethylene sorbitan monolaurate) (Atlas Europol, Ternate, Italy) were used to prepare the beads; sodium alginate (Fluka Chemie, Buchs, Switzerland) (MW about 115,000 as calculated from the Mark-Ouwink constants [5], mannuronate/guluronate ratio 0.43) was used to coat the beads. All the materials were used as supplied by the manufacturers and all the reagents were of analytical grade (Carlo Erba).

Preparation of the coated beads:

A) Preparation of the beads

The beads were prepared by extruding dropwise a NaCMC water solution (3%, w/v) containing ambroxol hydrochloride (3%, w/v) via a 4 cm 2-gauge needle by a 10 ml glass syringe. The extruded polymer containing the drug was dropped into a beaker placed on a magnetic stirrer. The beaker contained 10 ml of the curing solution ($AlCl_3 \cdot 6H_2O$, 60% w/v) dispersed in 20 ml of n-heptane using 0.1 g of Tween 20. Both the stirring rate (1,000 rpm) and temperature (25°C) were maintained constant throughout the curing procedure (5 min). The liquid phase was decanted and the formed beads were filtered, washed quickly with acetone and vacuum dried (10 mm Hg) for at least 48 hours.

To determine the free $AlCl_3$ not associated with the polymer, an exactly weighted amount of the beads was maintained at room temperature in deionized water for 48

hours. After recovering the beads, the amount of $AlCl_3$ in the water solution was assayed by titrimetric method according to the USP XXIII [6]. The amount of the free $AlCl_3$ (mean of 3 analysis) was 21.5±1.3% w/w (about 8×10^{-6} moles per each bead).

B) Coating of the beads

The beads were carefully added to a water solution of 2% w/v sodium alginate (corresponding to a 0.1M repeating unit solution) maintained under magnetic stirring (about 900 rpm) at a temperature of 25°C. The amount of sodium alginate used was greatly in excess of the free $AlCl_3$ contained in the beads (molar ratio between the repeating units of alginate and the free $AlCl_3$ about 60 : 1). Both the stirring rate and the discreet addition of the beads avoided the inclusion of two or more beads by a common coat.

The resulting coated beads were removed at fixed time intervals, quickly rinsed with water to eliminate any uncrosslinked sodium alginate fraction adhering to the coat and, then, with acetone to facilitate the drying process which was carried out under vacuum (10 mm Hg) for at least 48 hours.

The coated beads consisted therefore of an aluminum carboxymethylcellulose core and an aluminum alginate coat.

Analysis of the coating process

The coating process was analysed through an optical microscope (Carl Zeiss, Jena, Germany) by measuring the growth of the coat thickness and the variation of the core diameter as a function of time. All the data are averaged on four determinations.

Morphological and dimensional analysis

The morphology of the beads, of the coated beads and of their separated components (core and coat) was examined by scanning electron microscope (SEM) (XL-40, Philips, Eindhoven, The Netherlands).

The size of the beads, of the coated beads and of their cores was determined by optical microscope. The coat thickness was calculated through scanning electron microscope by measuring the cross-section of the coats in at least four areas. All the data are averaged on four samples from four different batches.

Element distribution analysis

The distribution of Al, Br and Na atoms in the beads and in the coated beads was evaluated by Energy Dispersive X-ray Analysis (EDS). As Al atoms can be the evidence of both the free $AlCl_3$ and the Al atoms involved in the crosslinking reaction, the distribution of the Al atoms involved in the crosslinking reaction was determined after having removed the possible free $AlCl_3$ fraction from the coated beads.

Sections of the samples were carbonated (model CED 010, Balzers Union, Liechtenstein) and analysed by EDS (EDAX 9900, Edax International, Prairie View, IL, U.S.A.) coupled with SEM. The emission maps of Al (1.49 keV), Br

(11.91 keV) and Na (1.04 keV) were obtained with the following experimental settings: 100x128 pixels; dwell time 200 msec; accelerating voltage 25 kV; detection limit about 0.3%.

Dynamic swelling

The dynamic swelling of the coated beads and of the cores separated from their coats was studied by allowing the samples to swell in deionized water at 25°C. The diameter of the dry samples (d_O) and their changes as a function of time were measured by microscopic method until the equilibrium swelling values (d_∞) were achieved [7]. All the experiments were carried out on four samples from four different batches.

Drug content

The drug content was determined in the beads, in the coated beads and in their separated components (core and coat) by dissolving a weighted amount of each sample in phosphate buffer solution (pH = 7.8).

The solutions were assayed spectrophotometrically (model Lambda 3B, Perkin-Elmer, Norwalk, CT, U.S.A.) at a wavelength of 245 nm. All the data are averaged on three determinations.

Drug release

Drug release from both the beads and the coated beads was performed in 100 ml of deionized water using a column-type apparatus (Apparatus 4 described in USP XXIII) (Dissotest CE-1, Sotax, Basel, Switzerland) at a flow rate of 25 ml/min and at a temperature of 37±0.2°C. All experiments were carried out under sink conditions using amounts of each sample corresponding to 3 mg of drug.

The released drug amount was determined spectrophotometrically at fixed time intervals. All the data are averaged on three determinations.

The release profiles of the coated beads were analysed by using a linear equation applied to the release data after the burst period.

RESULTS AND DISCUSSION

Analysis of the coating process

As the beads were soaked into a water solution of sodium alginate, a growing highly hydrated coat appeared around the swelling cores (Fig. 1). The coat was the result of the crosslinking reaction between sodium alginate in the solution and the free $AlCl_3$ diffusing from the bead.

The profiles of the dimensional variations of both the core and the coat observed during the coating process are shown in Figure 2. The biphasic profile of the changes in core diameter was previously justified by the combination of the processes of water penetration and solute diffusion [3]. On the contrary, the thickness of the coat increased monotonically. However, both the core diameter and the coat thickness reached the equilibrium values in about 60 min. Since the amount of sodium alginate used in the coating process was greatly in excess of the

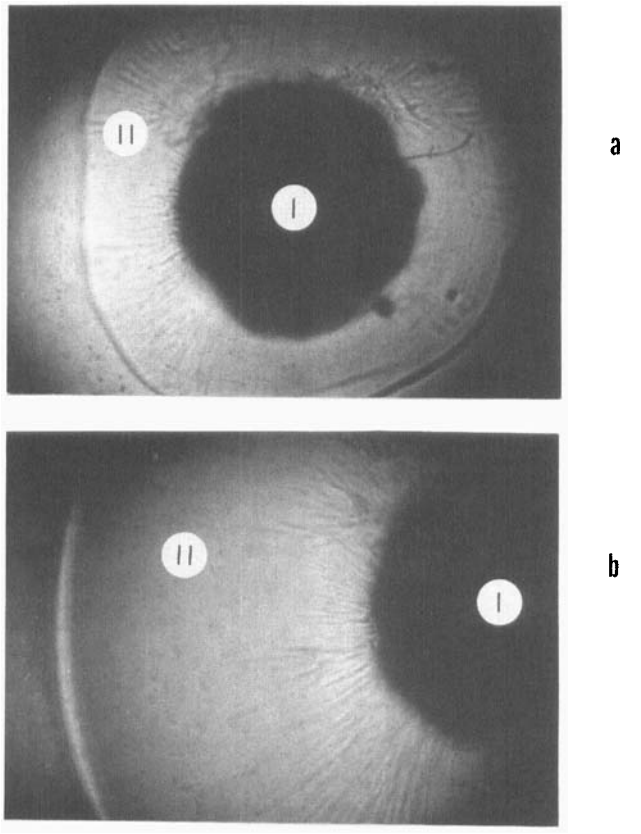

FIGURE 1
Optical photomicrographs of the coating process showing the core (I) and the growing hydtrated coat (II). Key: (a) 5 min of coating; (b) 30 min of coating. Scale bar: 0.5 mm.

free $AlCl_3$ contained in the beads, it is possible to exclude the depletion of the alginate in the solution. Therefore, the coat thickness increased and the core diameter decreased as long as the free $AlCl_3$ was present inside the bead. In fact, the coated beads obtained after 60 min of coating, analysed by titrimetric method [6], did not contain $AlCl_3$. Thus, the time period necessary to reach the equilibrium values (60 min) was the evidence of the complete diffusion of the free $AlCl_3$ from the bead. For this reason coating times higher than 60 min were not used.

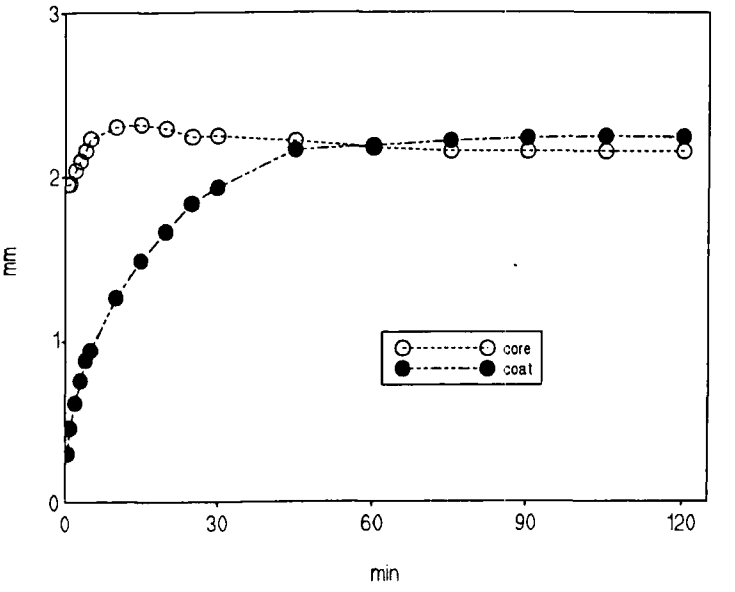

FIGURE 2
Dimensional variations of the coat thickness and the core diameter during the coating process.

Morphological and dimensional analysis

The coated beads showed a nearly spherical shape and a smooth surface (Fig. 3b), whereas the surface of the beads appeared rough (Fig. 3a). In order to investigate the internal morphology of the coated beads, the cross-sections of the cores and the coats were examined separately. Regardless of the coating time, the core showed a highly porous structure as that of the carboxymethylcellulose beads described in a previous work [3]. The coat obtained after 5 min of coating was fractured both in the surface and in the cross-section (Fig. 4a). On the contrary, the coat obtained after higher coating times appeared continuous and compact (Fig. 4b). Moreover, the coat appeared uniform in thickness, regardless the coating time.
The dimensional characteristics and the density values (calculated from the particle size data of samples having a known weight) of the samples are shown in Table 1.
The core diameter was found decreased in comparison with the diameter of the beads owing to the leaching of both the free $AlCl_3$ and the drug during the coating process, whereas the thickness of the coat increased with the increase of the coating time.
The sizes of the coated beads compared with that of their components denote a void space between the core and the coat, as also the translucence of the coat allows to observe by optical microscopy (Fig. 5a), known the coat thickness. Thus, the structural characteristics of the coated beads can be schematized as shown in

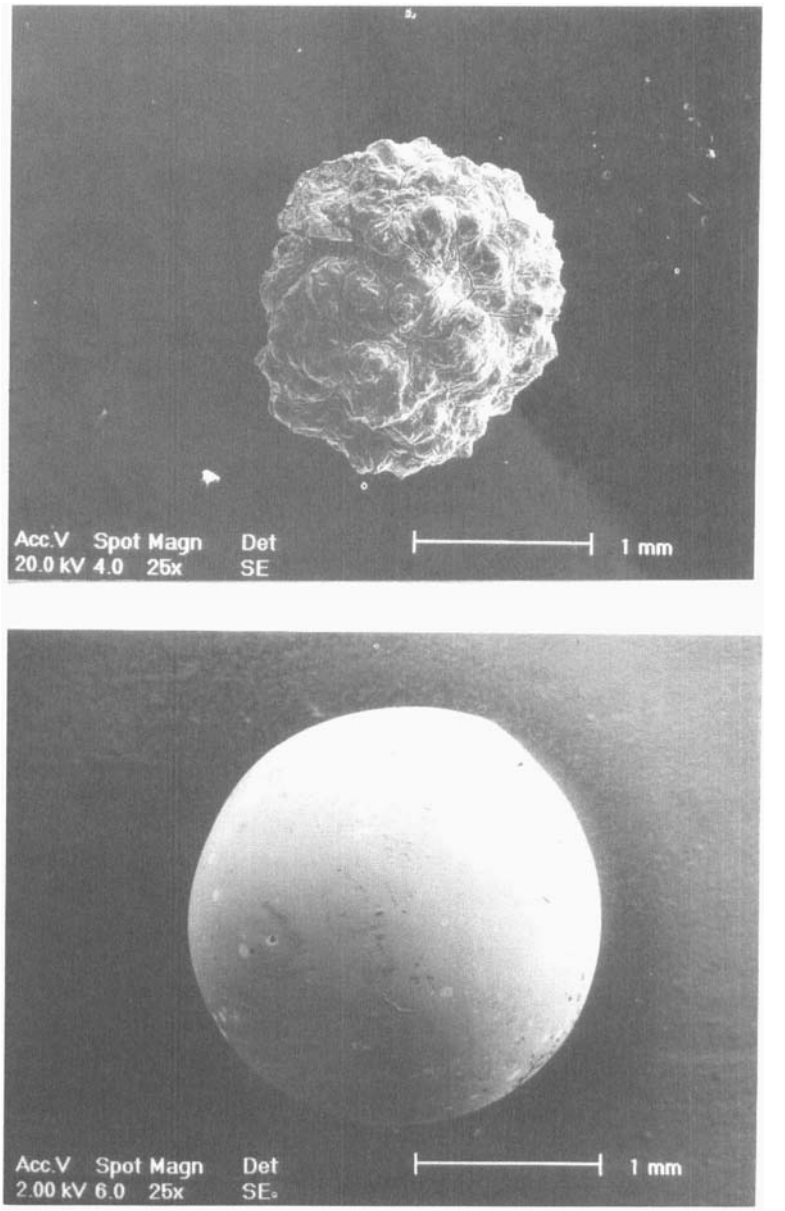

FIGURE 3
Scanning electron photomicrographs: Key: (a) uncoated bead; (b) coated bead (30 min of coating).

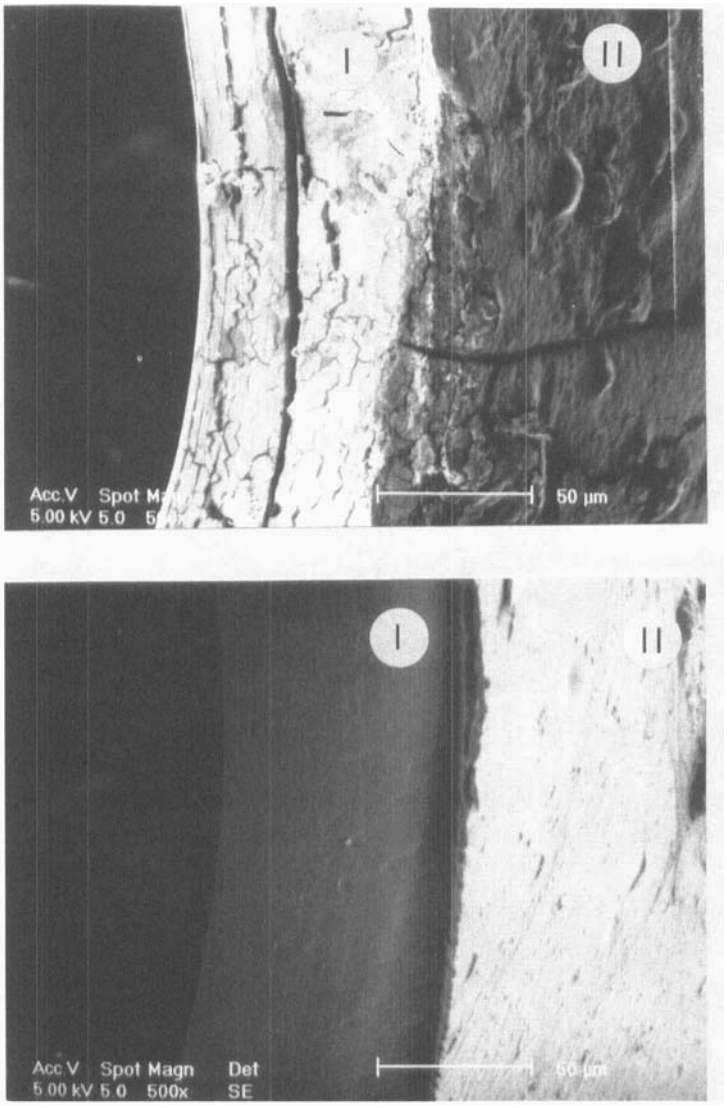

FIGURE 4
Scanning electron photomicrographs of the cross-sections of the coats separated from their cores showing the cross-section (I) and the outer toplayer (II). Key: (a) 5 min and (c) 15 min of coating.

TABLE 1
Dimensional characteristics of the beads (coating time = 0) and of the coated beads. Standard deviations in parenthesis.

Coating time (min)	Coated bead diameter (mm)	Core diameter (mm)	Coat thickness (μm)	Void space (mm^3)	Density (mg/mm^3)
0	1.8(0.1)	1.8(0.1)	-----	-----	1.70(0.10)
5	2.1(0.2)	1.4(0.1)	63(7)	2.6(0.3)	0.99(0.07)
15	2.4(0.2)	1.2(0.1)	77(1)	5.4(0.5)	0.68(0.06)
30	2.4(0.2)	1.0(0.1)	91(5)	5.5(0.7)	0.54(0.04)
45	2.6(0.2)	1.2(0.1)	113(10)	5.8(0.3)	0.46(0.03)
60	2.5(0.1)	1.1(0.1)	128(8)	5.6(0.2)	0.53(0.03)

Figure 5b. The void space could result from the deswelling of the core occurred during the drying process of the coated beads. In fact, the void space volume increased only up to 15 min of coating time corresponding to the time in which the core reached its maximum swelling value during the coating process (Fig. 2) and its minimum size in the dry state. According to this, the density of the RDM systems was lower than that of the beads and become <1 for coating times >5 min.

Polymer analysis by EDS

The EDS analysis of the coated beads showed the lack of Na atoms in both the core and the coat. In addition, the distribution of Al atoms involved in the crosslinking reaction appeared homogeneous both in the coat cross-section (Fig. 6b) and in the core cross-section, as previously reported for the carboxymethyl-cellulose beads [3]. These findings indicated that the Na substitution had taken place and the total crosslinking of both the polymers (NaCMC and sodium alginate) had occurred.

Drug content and distribution

The drug content of the coated beads was lower than that of the beads. Furthermore, as the coating time increased, the drug content and the drug content ratio between the core and the coat decreased (Table 2), as a result of the extraction of the drug during the coating process.

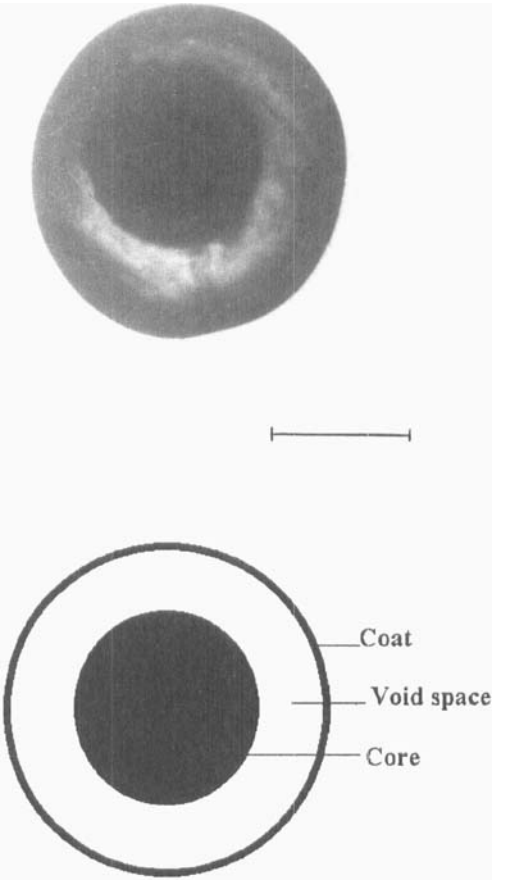

FIGURE 5
Optical photomicrograph (a) and schematic drawing (b) of a coated bead (30 min of coating). Scale bar: 1.0 mm.

The EDS analysis of the Br atoms, which are the evidence of the ambroxol hydrochloride, revealed the drug homogeneously distributed in the beads, as also observed previously [3]. On the contrary, the drug distribution appeared non homogeneous both in the core and in the coat of the coated beads. In fact, as the coating time increased, the drug was depleted from more internal areas of the core, whereas it concentrated in the periphery of the coat obtained after coating time higher than 15 min (Fig. 6c). These findings were probably the consequence of the drug migration through the system toward the alginate solution which enriched

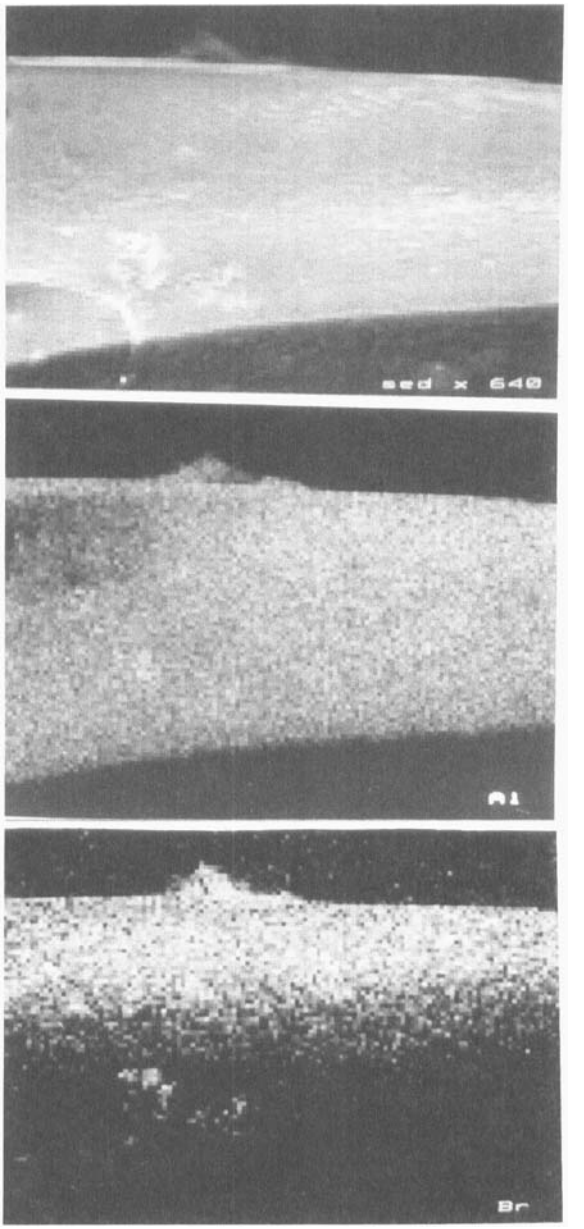

FIGURE 6
Energy Dispersive X-ray Analysis of a separated coat cross-section (30 min of coating). Outer toplayer at the upper side. Key: (a) scanning electron photomicrograph; (b) aluminum atom map; (c) bromine atom map.

TABLE 2
Drug content in the beads (coating time = 0), in the coated beads and drug ratio between the core and the coat. Standard deviations in parenthesis.

Coating time	Drug content		
(min)	(mg/coated bead)	(%, w/w)	core:coat ratio (%)
0	0.85(0.08)	16.4(0.2)	---
5	0.69(0.02)	13.1(0.2)	94: 6
15	0.64(0.02)	10.5(0.8)	81:19
30	0.36(0.06)	8.5(0.6)	56:44
45	0.22(0.04)	5.3(0.6)	52:48
60	0.14(0.01)	2.8(0.4)	50:50

with the drug. Thus, the crosslinking reaction occurred in a polymer solution containing an increasing amount of the drug.
Moreover, it is not possible to exclude that the evaporation condition of the solvent during the drying process can also affect the concentration distribution of the drug. In fact, only when the solvent is removed by a freeze-dry process the drug can maintain the concentration distribution acquired during the coating process [8-9].

Swelling behaviour
No swelling was observed for the coated beads owing to the alginate coat. In fact, alginate is known to do not swell in deionized water as well as in acidic medium [10].
Contrary to this, the carboxymethylcellulose cores, after the removal of the alginate coats, swelled in water. The dynamic swelling profile of the cores obtained after 5 min of coating was biphasic. The core diameter reached the maximum value ($d_{max}/d_0 = 1.17 \pm 0.01$) (about 10 min) before approaching the lower equilibrium swelling value ($d_\infty/d_0 = 1.10 \pm 0.01$). On the contrary, the cores of the coated beads obtained after higher coating times reached monotonically the equilibrium swelling value ($d_\infty/d_0 \cong 1.20$) in a range of 30-60 min. The change from the biphasic to the monophasic behaviour was the consequence of the decreased content of both the drug and the free $AlCl_3$, as previously justified [3].
Also, the swelling of the core could occurr freely, i.e. without physical restrictions by the coat, inside the coated beads, owing to the presence of the void space, as

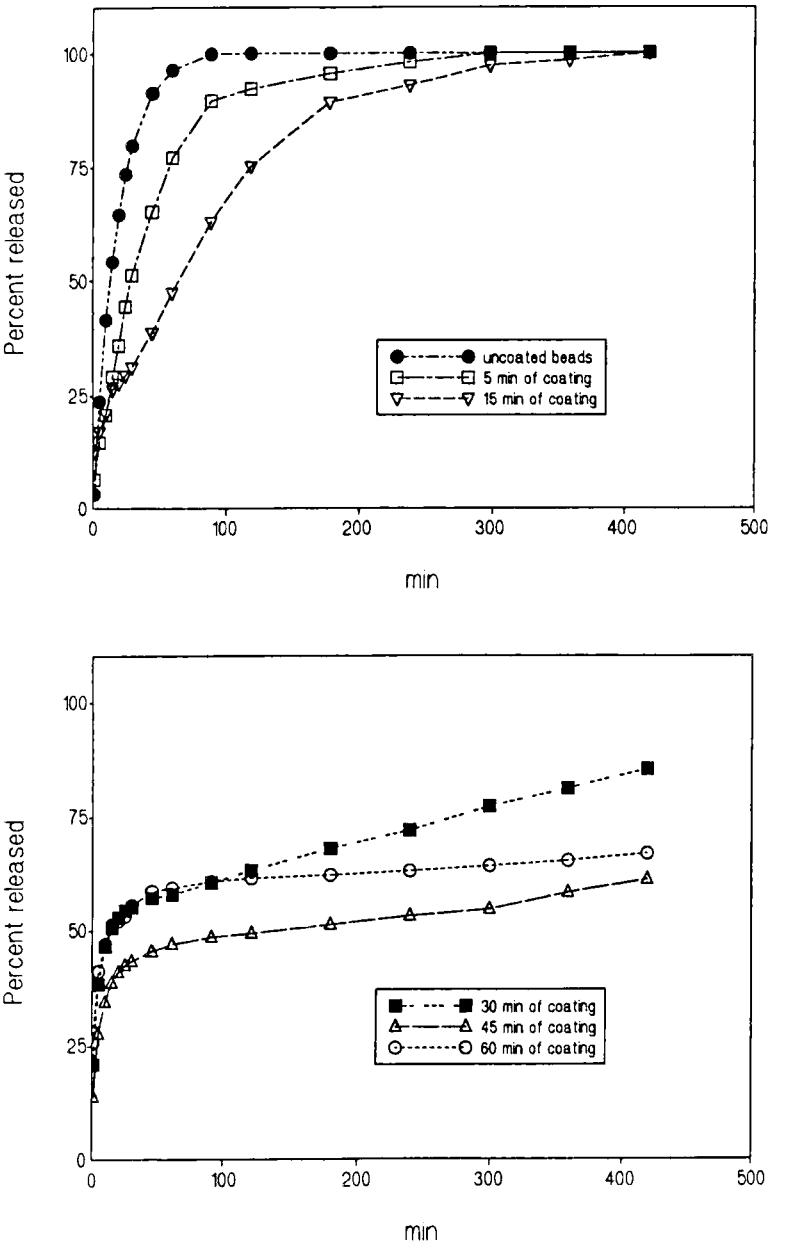

FIGURE 7
Release of ambroxol hydrochloride from the beads and the coated beads obtained with different coating times.

TABLE 3
Parameters of the release process according to the linear equation for the coated beads.

Coating time (min)	$k \times 10^2$ (min^{-1})	χ^2
5	1.36	0.0139
15	0.54	0.0070
30	0.08	0.0006
45	0.04	0.0007
60	0.02	0.0003

the size of the swollen cores less than the respective coated bead size suggests (Table 1).

Drug release

The release profiles of the drug from the beads and the coated beads are depicted in Figure 7.

The duration of the drug release from the coated beads was greater than that from the beads and increased with the increase of the coating time. However, a considerable burst period was observed for the coated beads obtained with coating times higher than 15 min. The burst phase may probably be due to the release of the drug fraction near the coat surface (see "Drug content and distribution"), though it does not appear related to the coating time period. Subsequently the burst phase, the coated beads gave a linear release. Also, with an increase in coating time (resulting in an increase in coat thickness), the rate of drug release decreased and the fitting of the relase data to the linear equation improved (Table 3).

This behaviour could be reasonable attributed to the presence of the alginate coat, whereas a control by the swelling of the core could be excluded. In fact, the most of the drug release in the linear phase occurred through a fully swollen polymer.

CONCLUSIONS

Coated beads were prepared by forming a crosslinked alginate coat on the surface of crosslinked carboxymethylcellulose beads.

The proposed coating technique is simple, rapid, mild and provides uniform coat thickness. Unlike the uncoated beads, the coated beads showed smooth surface, lower density values and prolonged drug release with a constant rate phase.
Moreover, by using such a coating technique, the removal of residual products of crosslinking reactions capable of affecting the drug release [3] or providing toxic effects, could be achieved.
By considering that the materials are nontoxic when taken orally, a possible application of these systems as controlled oral dosage forms could be evaluated.

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