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RESEARCH PAPER

Polysaccharides as Excipients for Colon-Specific Coatings. Permeability and Swelling Properties of Casted Films

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ABSTRACT

Oligosaccharides such as inulin (In) and polysaccharides such as galactomannans, combined with polymethacrylates on isolated films for film coatings, were obtained from aqueous-based solvents and investigated as potential vehicles for colonic drug delivery. These compositions, which are susceptible to fermentation by colonic microflora, constitute promising excipients for the development of new colon-specific therapeutic systems. The characteristics of several compositions have been demonstrated in permeability and swelling studies on isolated films composed of a polymethacrylate associated with In or galactomannans of mesquite seed gum (MSG). Results reported prove a dependency of the properties of mixed films on the polymethacrylate–polysaccharide concentration ratio and on the composition of the dissolution media. An increase in permeability through the mixed films was observed in a simulated colonic environment for the following compositions: Eudragit® RS30D–MSG 70 : 30 w/w; Eudragit® RS30D–In 90 : 10 w/w; Eudragit® RS30D–In 76 : 24 w/w.

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INTRODUCTION

The medical treatment of several pathologies with conventional dosage forms very often requires high doses and frequent drug administrations. During the last decades pharmaceutical research has shown an increased interest in the development of therapeutic systems, which could lead to a higher site specificity.

Oral therapeutic systems, which can delay the release of active compounds up to the colon, belong to these new developments (1). Colon-specific delivery systems can provide local treatment of several inflammatory diseases that affect the colon, in addition to perspectives on the absorption of proteins and peptides. These compounds are very sensitive to the gastrointestinal environment (e.g., analgesic peptides, growth hormone, insulin) and therefore cannot be administered orally.

Different approaches have been explored in order to realize a colon-specific drug release, including the synthesis of pro-drugs, the use of pH- or time-dependent degradable coatings, as well as biodegradable systems (2–4). In the case of the time-controlled release forms, the drug is released after a specific time interval based on the expected transit time for the device to reach the colon. But due to large variations in pH and transit times, neither principle is very reliable in terms of colon-specific drug release. Therefore, the specific enzymatic activity of the colon environment has been explored thoroughly.

Several natural polymers, such as those found in the diet, are preferred over synthetic materials for colonic delivery because they are safer and more available. Polysaccharides have recently been proposed as appropriate excipients for the development of colon-specific devices for oral administration based on their microbial biodegradability. A large number of these polysaccharides and oligosaccharides may form the basis for a suitable colonic biodegradable carrier (5–10). These polysaccharides present properties of film formation. However, they swell and become permeable in the presence of an aqueous environment, and some oligosaccharides have no film-forming properties. These problems can be overcome by incorporating a synthetic polymer used to formulate oral controlled-release and sustained-release delivery systems. These mixed films for coating formulations exhibit considerably changed properties, which may provide a means to deliver drugs to the colon (11).

Inulin (In) is an oligosaccharide found in plants such as onion, garlic, chicory, and Jerusalem artichoke. Its main applications range from a thickener, sweetener, and fat substituent in food products up to a diagnostic agent for the measurement of glomerular filtration rates. Due to its resistance to gastric enzymes and increased sensitivity to the medium of the colon, where it is affected by microflora fermentation, especially by *Bifidobacteria*, this oligosaccharide has been considered promising for colon-specific dosage forms (12,13).

Galactomannans from different vegetable species have been employed as pharmaceutical excipients, especially for different types of dosage forms with modified release properties, including colon specificity (14–17). The galactomannans extracted from mesquite seed gum (MSG) of *Prosopis juliflora*, DC, a Brazilian tree, contain high-viscosity hydrophilic polysaccharides with a galactose:mannose proportion of 1:4. These have been shown to possess physical and chemical properties similar to those of other commercial gums, which make them attractive to the food industry (18) and give them promising perspectives as a pharmaceutical excipient for film coating and matrix formation, both for modified release (19,20).

Aiming to develop a colon-specific drug delivery system, a series of candidate coatings on isolated films were formulated based on a synthetic polymethacrylic polymer in combination with either an oligo- or polysaccharide. A type of polymethacrylate, Eudragit®RS30D, which remains undissolved at any pH, was associated with two natural polymers: In or the galactomannans extracted from MSG.

The present investigation was therefore undertaken to study the behavior under different conditions of isolated films obtained from different mixtures in aqueous dispersion, containing Eudragit®RS30D and either MSG or In. Indeed, the isolated films technique has been described as being very useful in order to assess the properties of pharmaceutical coating materials (21,22).

Measurements of water vapor transmission (WVT) rate, degree of swelling, and permeability constitute simple evaluation methods for the in vitro determination of the characteristics of coatings (23). Moreover, the influence of polymeric composition due to the differences in molecular weight, as well as the effect of additives, can easily be demonstrated (24).

The resistance and accessibility of the mixed films to the fluids and constituents of the small intestine and colon, respectively, represent an indispensable condition for effective biodegradation in the colon environment. Therefore, swelling and permeability of the film must be such that a premature drug delivery can be avoided and the constituents of the membranes become gradually accessible to degradation in the colon. The guarantee of the absence of premature drug delivery, as well as accessibility to the microbial flora, is decisive for the real success of the system. Swelling is particularly determinative for the accessibility of the film to the microbial flora of the colon. It can be evaluated by the degree of swelling, while a too premature release can be demonstrated on the basis of film permeability.

MATERIALS AND METHODS

Materials

Highly-polymerized In (Raftiline® from Orafti, Tiense Suiker, Tienen, Belgium), galactomannan extracted from MSG (Supranor®, Recife, Brazil), Eudragit®RS30D (RS30D) (ammonium methacrylate copolymer, type B, USP/NF) from Röhm Pharma (Darmstadt, Germany), triethyl citrate from Sigma-Aldrich® (Bornem, Belgium), and caffeine (Pharm. Eur.) from Federa (Brussels, Belgium). Simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) were prepared according to the *USP*, 23rd ed. (1995). For the digestibility studies in simulated colonic fluid (SCF) either a galactomannase (Gamanase®, CHN01009) or an inulinase (Fructozyme®, KIN00023) from Novo Nordisk® (Bagsvaerd, Denmark) were added to the buffer solutions. All other reagents used were of analytical grade.

Methods

Film Preparation

Isolated films were prepared by a process named "casting and evaporation." Aqueous dispersions (3% m/v) of In or MSG galactomannans were mixed with RS30D and triethyl citrate, which was added as a plasticizer (20% w/w of the methacrylate copolymer) under stirring for approximately 5 hr. After complete homogenization the dispersions were sonified and the remaining air evacuated under vacuum. Samples of volume 10 mL were poured over Teflon®-covered glass plates within circles previously marked out with silicon. The glass plates were stored for 10 hr in an air-circulated oven at 60°C, corresponding to the minimum film formation temperature (MFFT). The films obtained were carefully removed from the substrate and macroscopically examined for the presence of air bubbles and cracks, transparency, and flexibility. Thickness was determined using a micrometer (Lorentzen & Wetters®, Van der Heyden, Brussels, Belgium).

Water Vapor Transmission Study

The study of WVT was carried out according to method B of ASTM designation E96-66 using Payne permeability cups (Braive Instruments, Liège, Belgium). Demineralized water (10 mL) was put into one of the cups, and the film was subsequently attached to the device. The cup with the film was then weighed and stored in a desiccator filled with silica gel. After 24, 48, 72, 96, and 120 hr of storage the cups were reweighed in order to determine the permeated amount of water (mass loss percent).

The different values of mass loss were fitted to Eq. (1) and standardized to a 24-hr time period, establishing the WVT for each polymeric composition tested (23):

$$\mathrm{WVT} = g \times 24/t \times a \tag{1}$$

where g represents mass loss, t is time (measured in hours during which the weight loss occurred), and a is the exposed area of the film (10 cm^2).

Determination of Swelling Index

Isolated films, corresponding to different compositions, were cut into pieces of about 1 cm^2 and placed in a vacuum oven at 70°C for complete drying for approximately 15 hr. The dried samples were stored in desiccators.

Individual dry film pieces were weighed and immersed in different liquid media, such as SGF and SIF, for different periods of time. During the first 10 min the samples were removed every minute, dried between two filter paper sheets, and weighed. After this period sampling was set at every 30 and 60 min.

The swelling behavior of the films was quantified using Eq. (2), suggested by Blanchon et al. (25):

$$I_s(\%) = (M_s - M_i)/M_i \times 100 \quad (2)$$

where I_s is the swelling index, M_s is the film mass after a certain swelling period, and M_i is the dry film mass.

Permeability Study

Films of different compositions were individually mounted between the acceptor and donor compartments of a diffusion cell (SM16750, Sartorius®, Van der Heyden, Brussels, Belgium).

In the closed circuit, either SGF or SIF was circulated at 20 cycles/min at 37°C (±0.5). The initial concentration of caffeine diffusing from the donor to the acceptor compartment was 0.0724 M. In samples collected in the acceptor compartment every 10 min, the amount of caffeine that migrated from the donor compartment through the film to the acceptor compartment was determined spectrophotometrically at 274 nm.

For the characterization of the susceptibility of the films to biodegradation, the system was filled with either phosphate buffer pH 6.8 (SCF) or acetate buffer pH 4.5. The speed of the liquid circulating through the closed circuit was reduced to 3 cycles/min. Gamanase® enzymes (0.1 mg/mL) were added to the phosphate buffer for the films containing galactomannans, while Fructozyme® enzymes (3 units/mL) were added to acetate buffer pH 4.5 for the film containing In. Samples from the acceptor compartment were collected each hour during 18 hr.

As reported by Van den Mooter et al. (23), caffeine diffusion through the films can be described using "quasi-stationary" state conditions (26). The diffusion rate through the membrane can be expressed by Fick's first law. The permeability coefficient P (cm/sec), can be calculated using:

$$(2PS/V)t = -\ln(\mathrm{Co} - 2\mathrm{Ca})/\mathrm{Co} \quad (3)$$

RESULTS AND DISCUSSION

Water Vapor Transmission

A statistically significant ($p < 0.05$) difference was found between the values of WVT (Table 1) for the different compositions studied. An increase in WVT was found for the following series: RS30D:MSG 70:30 > RS30D:MSG 80:20 > RS30D:MSG 90:10 > RS30D:In 76:24 > RS30D:In 90:10.

Table 1

Rates of WVT in Function of Film Composition

Film Composition (% w/w)	WVT ($g/24\,hr\,m^2$)	g/t (g/h)
RS:MSG 90:10	500.2	0.020842
RS:MSG 80:20	676	0.028167
RS:MSG 70:30	755.8	0.031492
RS:In 90:10	283.6	0.011819
RS:In 76:24	320.4	0.01335

RS = Eudragit®RS30D; MSG and In = 3% solution in water of MSG or In.

The results (Table 1) demonstrate that WVT is affected by the composition of the film and depends on the nature of the polysaccharide added, as well as on the concentration used. An increase in polysaccharide concentration significantly influences ($p < 0.05$) WVT. The registered phenomenon is justified by the increase in hydrophilicity caused by polysaccharide addition, an effect mainly observed in the membranes containing MSG.

Van den Mooter et al. (23), while working on colon-specific azo polymers, observed an increase in the WVT rate with increased hydrophilicity of azo polymers. Similarly, the incorporation of a polysaccharide into a Eudragit®RS30D film engenders an increase in hydrophilicity. Yet MSG, which has the highest water solubility (18,27) and accordingly the highest hydrophilic character, gives a higher increase of WVT compared with In, which is known to have low water solubility.

Determination of Swelling Index

Swelling levels (I_s%) were measured in order to determine the degree of hydration of the membranes.

The results of the swelling experiments are combined in Figs. 1 and 2 SGF(G) and SIF(I), respectively. As expected from the results of the WVT experiments, films containing the highest concentration of the most hydrophilic polysaccharide reach the highest degree of swelling. Incorporation of MSG into Eudragit®RS30D films leads to a much larger swelling than In. This statement is valid for both simulated media.

The potential advantage of the associations of synthetic and natural polymers is based on the maintenance of their integrity through the gastrointestinal environment, due to their non-digestibility properties in this part of the digestive tract.

The presence of a gel layer on the surface of the immersed film samples became visible after addition of MSG, and less so in the presence of In. This phenomenon may be an indication of a higher accessibility of the constituents of the external media to the membrane. In this case, the first polymer association should give the highest susceptibility to fermentation by specific enzymes of the colon flora.

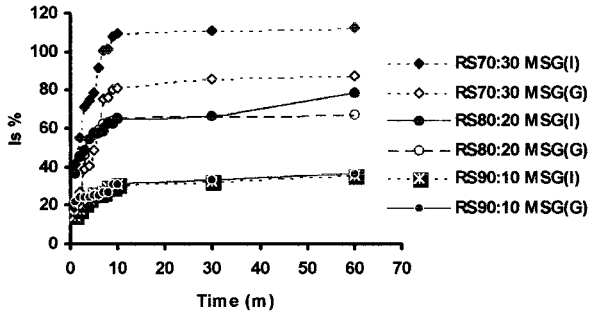

Figure 1. Swelling index (I_s) in SGF(G) and SIF(I) for different associations of Eudragit® RS30D:MSG.

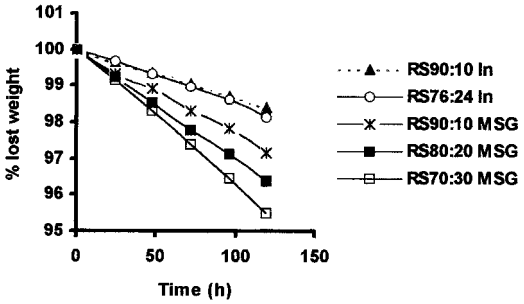

Figure 2. Swelling index (I_s) in SGF(G) and SIF(I) for different associations Eudragit® RS30D:In.

An increase in polysaccharide concentration resulted in a statistically significant ($p < 0.05$) increase in degree of hydration of the films, which was the highest for the combinations: RS30D:MSG 70:30 and RS30D:In 76:24.

A supplementary rise in hydration was also observed when the films were immersed in the more neutral buffer solution, which simulates the SIF. This increase in hydration could be attributed to structural alterations in the polysaccharides in a more neutral medium, especially MSG, for which the rise is more marked. This agrees with the data from Goycoolea et al. (28) who, on evaluating the viscosity of galactomannans under alkaline pH, registered alterations of their behavior in solution as steric expansion, and electrostatic repulsions between the constituent chains.

Permeability Studies

Tables 2 and 3 list the average values of the permeability constants for caffeine with different polymer combinations. Caffeine was used as a model drug because of its high ultraviolet (UV) absorbance and non-ionic character (24,29). Both SGF and SIF were used as a solvent for this tracer. The acceptor compartment was filled with the same liquid.

Table 2

Permeability of Caffeine in Eudragit Films Containing MSG or In

	Permeability Coefficients (cm/sec)	
Associations	SGF	SIF
RS:MSG 90:10	1.91×10^{-8} (±0.18)	1.43×10^{-7} (±0.17)
RS:MSG 80:20	2.09×10^{-7} (±0.09)	7.411×10^{-6} (±0.08)
RS:MSG 70:30	4.23×10^{-7} (±0.19)	9.91×10^{-6} (±0.18)
RS:In 90:10	1.43×10^{-9} (±0.20)	3.62×10^{-9} (±0.22)
RS:In 76:24	1.91×10^{-8} (±0.19)	7.25×10^{-8} (±0.21)

The standard deviation is given in parentheses ($n = 3$). SGF = simulated gastric fluid for 2 hr; SIF = simulated intestinal fluid for 4 hr.

Table 3

Permeability of Caffeine Through Eudragit Films Containing MSG or In in SCF With or Without Gamanase® or Fructozyme®

	Permeability Coefficients (cm/sec)	
Association	SCF (−enzyme)	SCF (+enzyme)
RS:MSG 90 : 10	5.77×10^{-7} (±0.18)	5.97×10^{-7} (±0.20)
RS:MSG 80 : 20	1.73×10^{-5} (±0.17)	1.80×10^{-5} (±0.18)
RS:MSG 70 : 30	3.70×10^{-5} (±0.12)	5.87×10^{-5} (±0.11)
RS:In 90 : 10	4.78×10^{-9} (±0.24)	9.55×10^{-9} (±0.19)
RS:In 76 : 24	4.85×10^{-7} (±0.04)	2.17×10^{-6} (±0.05)

The standard deviation is given in parentheses ($n = 3$). SCF = simulated colonic fluid for 18 hr, 3 cycles/min.

This closed system enables an appropriate study of the evaluation of the film behavior in simulated media, for instance the influence that polysaccharides have on the membrane compositions.

The permeability of the mixed films remains very low in SGF, as well as in SIF, as long as the concentration of the polysaccharides added is low, indicating that the insolubility of the film as given by Eudragit®RS30D is maintained. An increase in the amount of polysaccharide (compositions Eudragit®RS30D:MSG 80:20 and 70:30) induces an increase in diffusion. The same observation was also made for the presence of In, although the permeability values remain much smaller than those for MSG.

To investigate the digestibility of the films containing MSG and In by an enzymatic breakdown, specific enzymes were added to SCF; a galactomannase for MSG and an inulinase for In (Table 3).

In the absence of enzymes in the SCF the following permeability increase was noted: RS30D: MSG 70:30 > RS30D:MSG 80:20 > RS30D:MSG 90:10 > RS30D:In 76:24 > RS30D:In 90:10. For those films tested using enzymes simulating a colonic environment, the compositions RS30D : MSG 90:10 and RS30D:MSG 80:20 showed differences in the value of their permeability coefficient. However, those differences were not significant ($p < 0.05$) when compared with the values obtained under the control conditions. The increase in permeability to caffeine was found to be proportional to the increase in polysaccharide concentration. The enzyme was mainly effective at the higher polysaccharide concentration, especially in those membranes containing In.

Similar results were obtained by Vervoort et al. (12) for In associated with Eudragit®RS100. An increase in the In content of the film results in an increase in the permeability and consequently in the digestibility by specific enzymatic attack.

Referring to Hogan (30), Vervoort et al. also argue that another possible cause of the observed permeability increase might be the interference of the higher charges of solid material with the film formation process, leading to defects in the internal structure of the films. This could be justified mainly in In cases due to its difficulty to dissolve at room temperature.

In this study, we get around the problem of the low solubility of In in aqueous media at room temperature by heating the dispersion of In in RS30D at 40°C. This led to complete dissolution of In and to film formation under higher blending conditions.

In our case, this permeability increase could be explained firstly as a direct consequence of swelling levels presented by the different categories of proposed membranes. This hydration level favored enzyme accessibility to the film components, later permitting an enzymatic decomposition with consequent permeability increase due to the formation of pores or fissures in the tested membranes.

The increase in film susceptibility to enzymatic attack corresponds to the increase in polysaccharide concentration. The most evident results (Table 3) of this enzymatic attack were registered in the compositions RS30D:MSG 70:30, RS30D:In 90:10, and clearly for the films containing In, as in the composition RS30D:In 76:24.

CONCLUSION

The study has shown that the incorporation of polysaccharides or oligosaccharides into polymethacrylate aqueous dispersions leads to mixed films with considerably changed properties, which provide a possible means for delivering drugs to the colon.

The polymethacrylate component, which was present in the highest concentration, functioned as a basic polymer and permitted films to be obtained that resisted SGF and SIF. An increase in the amount of added polysaccharide or oligosaccharide favored the degree of hydration and swelling, and also enzymatic attack.

These factors argue in favor of access of the constituents present in the colon environment to the polysaccharide or oligosaccharide present in the films. This fact allows the expectation that such coatings will be able to direct solid dosage forms to the lower regions of the gastrointestinal tract, where the component of natural origin, the polysaccharide or oligosaccharide, incorporated into the mixed film, will be digested. This digestion would allow the delivery of the drug(s) present in the dosage form. Further research using in vivo experiments is needed to prove the delayed drug delivery.

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