ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 291–297

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

The formation of colonic digestible films of amylose and ethylcellulose from aqueous dispersions at temperatures below 37°C

C.W. Leong[a], J.M. Newton[a,*], A.W. Basit[a], F. Podczeck[a], J.H. Cummings[b], S.G. Ring[c]

[a]*School of Pharmacy, University of London, London, UK*
[b]*The Dunn Institute of Clinical Nutrition, Hills Road, Cambridge CB2 2DH, UK*
[c]*Institute of Food Research, Norwich Research Park, Colney, Norwich NR4 7WA, UK*

Received 15 October 2001; accepted in revised form 21 August 2002

Abstract

The film forming properties of a commercial aqueous ethylcellulose dispersion (Surelease) mixed with a range of ratios of an amylose/butanol complex in the presence of a range of concentrations of a plasticiser has been studied by measuring the minimum film forming temperature (MFFT). Contrary to what was to be anticipated from the literature, it was found that an additional 4% of the plasticiser (dibutyl sebacate), normally present in the standard formulation of the ethyl cellulose dispersion, was sufficient to lower the MFFT to allow the formation of films at 35°C. This was confirmed by assessment of the glass transition temperature of free films prepared by casting and drying at 35°C by the application of dynamic mechanical analysis. This technique also demonstrated that the ethylycellulose and the amylose were not miscible. The ability of faecal slurry to digest the films formed at low temperatures was confirmed by the use of a batch fermenter. The extent of digestion was directly related to the amylose content of the films, ensuring the potential to provide films, which could function as colon specific coatings.

Keywords: Amylose; Colon delivery; Dynamic mechanical analysis (DMA); Ethylcellulose dispersion; Minimum film forming temperature (MFFT); Plasticiser

1. Introduction

The application of films containing amylose and ethylcellulose as a specific colonic delivery system has been described by Milojevic et al. [1,2] and Cummings et al. [3]. The preparation of such films was undertaken with the dispersion heated to temperatures above 60°C before spraying and using air inlet temperatures in the fluid bed coater in excess of 40°C. The use of such temperatures arises from the involvement of both an aqueous dispersion of ethylcellulose and an aqueous/butanol dispersion of amylose. The reasons that these systems both require elevated temperatures, differs for the two systems. These will now be considered.

1.1. Ethylcellulose

When placed in an aqueous environment, films prepared from amylose swell and become permeable. To overcome this problem, ethylcellulose was added to the system [1–3]. Ethylcellulose is an ethyl-substituted cellulose ether, where the glucose units are joined by β-1,4 links. The ethoxyl substitution values of commercial products range from a degree of substitution of 2.2–2.6 ethoxyl groups per anhydrous glucose units. This corresponds to an ethoxyl content of 44.5– > 49% [4]. Ethylcellulose is hydrophobic and has been successfully formulated into commercially available aqueous coating dispersions.

1.2. The mechanisms of film formation from ethylcellulose coating dispersions

These commercially available aqueous coating dispersions contain discrete ethylcellulose spheres. Each of these ethylcellulose spheres, with less than 1 μm in diameter, contains hundreds of ethylcellulose chains. During deposition of these discrete spheres onto the surface, the water evaporates, the dispersion is condensed and the ethylcellulose particles become closely packed. If the condition favours coalescence, these particles would become deformed and fused together to form a film [5]. The formation of a homogenous film from an aqueous dispersion of discrete ethylcellulose spheres is a complex, multistage process [6].

* Corresponding author. School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, UK.
E-mail address: michael.newton@ulsop.ac.uk (J.M. Newton).

0939-6411/02/$ - see front matter
PII: S0939-6411(02)00121-2

The initial stages of coalescence would only occur if the various strong driving forces overcome the inherent hardness of the ethylcellulose spheres and their repulsive electrostatic forces. Various models have been proposed to explain the driving forces, which cause coalescence of these polymeric spheres to occur. These are reviewed in detail in the literature [5,7,8].As more water is driven from the closely packed polymeric particles, a strong capillary pressure, located among interparticulate contact points, is generated. This pressure compresses the polymeric particles and forces them to fuse. How far particle fusion can proceed at this stage would depend on the rate of disappearance of the aqueous phase in addition to the surface tension and mechanical properties of the polymeric phase. After water is completely evaporated, the pressure caused by water-polymer interfacial tension is replaced by air-polymer surface tension. This new pressure forces the polymers to fuse further, provided the polymeric particles are deformable. A dry, transparent, apparently continuous film is formed. This is generally accepted as the first stage of the process of coalescence.

The second stage, often considered to occur after the coating process, is a gradual completion of coalescence observed during ageing of the film. A post coating high temperature treatment may speed up this process, which is time and temperature related. This process of stabilisation of the film coat is known as curing [9–11].

1.3. The heat requirement for the formation of ethylcellulose film

Both the first and the second stages of coalescence involve energy. Sheetz [6], using the thermodynamic analysis of latex film formation theory, pointed out that the most important source of energy in ensuring particle fusion is the environmental heat energy. Heat is converted to useful work by evaporation of the water to overcome the repulsion forces to form a film. Satisfactory film formation depends on the prevailing temperature at which film formation is to take place. The minimum temperature below which the polymer particles do not possess sufficient energy to coalesce into a film is known as minimum film forming temperature (MFFT). The value of the MFFT is influenced by a number of factors, including the Tg of the polymer component. The relationship between the polymer Tg and the MFFT is complex as the MFFT is a property of the entire latex formulation and not just the polymer phase [12,13]. One of the coating formulation additives shown to affect the MFFT is the plasticiser. Effective plasticisers tend to lower the MFFT of the coating dispersion. The MFFT of the ethylcellulose dispersions has been shown to be successfully lowered using various plasticisers to around 40°C [9,14]. Nevertheless, these plasticised ethylcellulose dispersions still required high coating temperatures, i.e. higher than 37°C to achieve complete coalescence [14–17].

1.4. Amylose

Amylose is defined as that starch polysaccharide which binds 19.5% of its weight of iodine at 20°C [18]. It is the high molecular weight component of starch and is made up of α-1,4-bonds and is essentially linear although evidence is now accumulating that some amyloses may contain a few very long branches [19,20]. The degree of polymerisation of natural amylose can vary from 300 to 3000, depending on the botanical origin. The amount of amylose usually present in starch is between 20 and 35%, although breeders have managed to develop starches, which contain no amylose (waxy type) or those, which contain between 50 and 80% amylose [21].

1.5. The formation of glassy amylose film

Amylose can be extracted from starch by an aqueous leaching process [22,23]. The extraction process involves leaching an aqueous slurry of raw granular starch above its gelatinisation temperature. When heated above the gelatinisation temperature, the granular order is lost. The granules swell to many times their original size and amylose is preferentially solubilised. The solubilised amylose in water is separated from other insoluble granular starch fractions by centrifugation and filtration. The amylose solution is then further purified and stabilised with the addition of butan-1-ol. The final product is an aqueous amylose/butanol complex dispersion. The aqueous complex dispersion is used as a coating material. A schematic representation of how amylose in the form of an aqueous amylose-butanol complex dispersion is converted to glassy amylose is shown in Fig. 1.

Glassy amylose would be successfully formed only when the preceding stages are well controlled. Therefore, an understanding of each stage is vital. The first stage involves the regeneration of amylose solution from amylose-butanol complex dispersion. The temperature required to melt the complex would depend on the nature of the complex, i.e. crystalline ($Tm = 68°C$) or amorphous ($Tm = 48°C$) [24]. Generally, it is preferable to form amylose film from regenerated amylose solution, as films cast from the dispersion are usually hazy in appearance rather than being completely clear [25].

Once the metastable amylose solution is formed, depending on its concentration, as it cools, either a gel or a precipitate would form. Below a concentration known as the coil overlap concentration, C*, a precipitate would form. Above C*, a gel would form. The value of C* is dependent on the linearity and degree of average polymerisation [23]. If gelation is favoured, as the amylose solution cools, the amylose chains reassociate or retrograde leading to phase separation of polymer rich and polymer deficient regions. In the continuous polymer rich phase, the molecular level re-association of amylose chains results in the supermolecular formation of amylose filaments. These filaments are assemblies of many

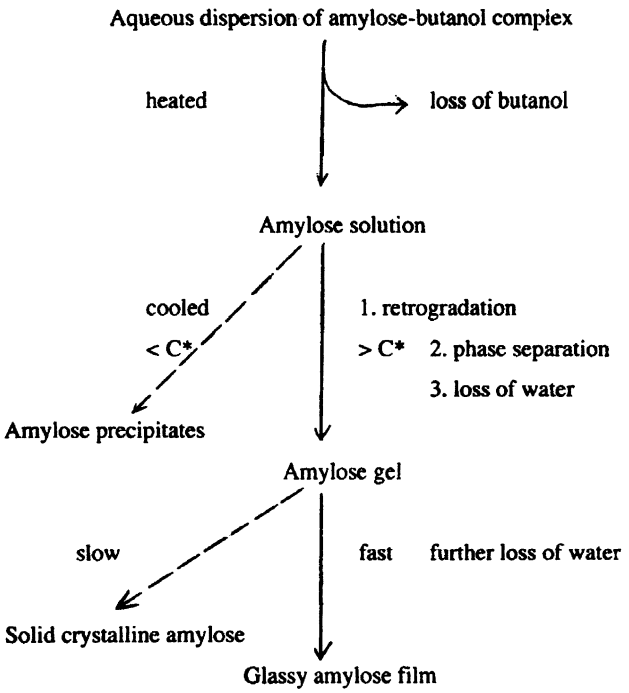

Fig. 1. Schematic representation of amylose film coating formation from an amylose-butanol complex dispersion. C* is the coil overlap concentration.

amylose chains. The filaments form an interpenetrating matrix structure, i.e. a gel [26–28].

Upon further rapid drying of the gel, the amylose filaments pack more densely forming a glassy amylose film. The formation of any glassy material can be visualised as follows: as the solution forms a super-cooled liquid, there is a simultaneous increase in viscosity, until at a temperature known as the glass-transition temperature, Tg, when the viscosity is around 12 Pas, the liquid-like structure is 'frozen in'. The polymer chains in the liquid-like structure are not packed in a regular manner; hence, a glassy, amorphous material is formed. The main determining factor of whether a glassy or crystalline material is formed is in the rate of drying. If a very slow drying rate is used, the polymers have sufficient time to reorganise in a regular manner; hence, a partially crystalline material is formed. During the coating process where rapid drying is essential, only glassy amylose is likely to be formed.

1.6. The reasons for the specificity of glassy amylose for colonic delivery

Glassy amylose was chosen for oral colonic delivery because not all forms of amylose are resistant to digestion in the upper gastrointestinal tract (GIT). For example, amylose solution and amylose found in the starch granules are not necessarily resistant. Only retrograded amylose resists upper gastrointestinal (GI) digestion by pancreatic amylases [29–31]. In retrogradation the free amylose chains are re-associated. The amylose chains become entangled and the intra- and inter-molecular hydrogen bondings of amylose reduce their flexibility to fit into the active site of the enzymes making retrograded amylose resist digestion in the upper GIT [32,33].

Apart from the inherent resistance of amylose due to inter- and intra-molecular hydrogen bonding, a second mechanism of resistance involving filaments of amylose was also proposed [33,34]. Amylose filaments are formed when a large number of reassociated amylose chains are assembled. These 20 nm wide filaments form a three dimensional network which can be viewed under standard error of the mean [35]. As the degree of entanglement increases, the rate and extent to which the enzyme can diffuse into the core of the amylose substrate decreases. This leads to a further decrease in the hydrolysis of amylose.

1.7. Glassy amylose is a form of retrograded amylose, which is believed to resist upper

GIT digestion by both these mechanisms [34]. However, once the upper GIT resistant amylose is passed into the colon, it is digested by the bacterial microflora [29,32,36]. The end products are shown to be fatty acids and non-toxic gases. The amylose, which escapes digestion in the upper GIT, can be digested by the colonic microflora because bacterial cell-bound amylases are considerably more efficient than the pancreatic amylases in the initial stages of starch hydrolysis [37]. The difference in efficiency of mammalian and microbial α-amylases could be explained in terms of the enzyme structure. In addition to its increased efficiency, there is an abundance of these enzymes in the colon to aid digestion of resistant amylose. Macfarlane and Englyst [37] have shown that there is a group of amylolytic bacteria, rather than just one species, which is responsible for the amylolytic activity. These amylolytic bacteria make up to over 50% of the bacteria count of faeces. Therefore, it is not surprising that the amylose could be digested in the colon. These amylolytic activities are not uniformly distributed along the colon but are highest in the caecum and ascending colon [38,39], allowing drug from amylose-coated dosage forms to be released all along the colon.

1.8. The heat requirements for the formation of glassy amylose

During the formation of glassy amylose, the highest input of heat energy occurs in the regeneration of the amylose solution from amylose-butanol complex dispersion. The aqueous amylose-complex dispersion has to be heated to ~70°C to melt the complex. Once amylose solution is formed, it has to be maintained at a high temperature to prevent it from solidifying. Hence, the coating material was sprayed at 60°C to prevent clogging of the spray nozzle. These steps would have to be omitted to achieve formulations suitable for low temperature coating.

Thus from a consideration of the literature, it would not be anticipated that the films prepared from mixtures of Sure-

lease and an aqueous dispersion of amylose, which would be colon specific in its release properties, could not be prepared unless they were formed at temperatures in excess of 37°C. Under these conditions heat labile materials such as enzymes and bacteria, which could be used to treat the colon, would be inactivated. The aim of the current work was to establish whether in fact this was the case.

2. Materials and methods

The aqueous amylose/butanol complex dispersion was supplied by the Institute of Food Research, Norwich, UK and had a solids content of 6%. The amylose was extracted from smooth pea starch (Nastar, Cosucra, Belgium) as described by Adkins and Greenwood [22]. The aqueous ethyl cellulose dispersion was Surelease grade EA7100 (Colorcon Ltd, Dartford, UK). This is the direct replacement for the Ethocel reported in previous publications [1,2] and contains a total solid content of 25% of which 19% is ethylcellulose. The mixtures of amylose and Surelease are expressed as the ratio of the solid amylose to ethylcellulose present in the two dispersions. The dibutyl sebacate (DBS) was of reagent grade (Sigma Chemicals, Poole, UK). All other chemicals were of analytical grade (Merck Ltd., Poole, UK).

2.1. Determination of the minimum film forming temperature (MFFT)

A modified ASTM D 2354-91 MFFT apparatus was constructed. The single container was divided into four equally sized sections to increase the number of samples, which could be tested on one occasion. The number of temperature sampling points was increased to improve the accuracy of the assessment. Care was taken to ensure that the device was level, a fixed quantity of the aqueous dispersion was spread evenly along the channels and the temperature gradient was maintained by keeping the cold water bath at one end of the bar set at 3 + 1°C while the other end was maintained at temperatures between 20 and 46°C, depending on the sample being tested. The need for different temperatures for this water bath was to try and ensure that the MFFT was not too close to the end of the equipment. The results therefore do not always provide precise values for the MFFT at the lower and upper ends of the temperature scales. A value of the MFFT below 12°C would allow the films to form at temperatures of about 22°C (a suitable temperature for enzymes or bacteria). If values below this temperature were obtained, no further experiments were carried out. Similarly, if temperatures above 30°C were found, such values would require coating temperatures in excess of 40°C, i.e. too high a temperature. All experiments were carried out in duplicate.

2.2. Preparation of cast films

While the films prepared by casting can differ from those produced by spraying, the initial experiments were carried out on cast films as these represent the conditions used to determine the MFFT. One could expect spray films to respond in a similar way to the changes in plasticiser concentration.

Cast films were prepared from appropriate dispersions by pouring into circular wells cut to give a smooth surface in polytetrafluoroethylene (PTFE) blocks, drying in a hot air oven (Hotbox, Gallenkamp London, UK) at 35°C, to constant weight. The thickness of the films was maintained as uniform as possible by the use of dispersions containing a constant total amount of solids. The films were stored at 20°C and 44% relative humidity (RH) for 7 days before testing.

2.3. Dynamic mechanical analysis (DMA)

The cast films were tested in compression mode between 3 mm diameter stainless steel parallel plates with a Perkin-Elmer DMA-7 Analyser (Perkin-Elmer, High Wycombe, UK). Initial dynamic stress scans were undertaken on the various film samples to determine the best test conditions for measuring the value of Tg. The temperature was maintained at 25°C, with a static force of 2100 mN at a scan rate of 20 mN per min over the scan range of 10–1000 mN. These test indicated that, with static force of 2100 mN, dynamic conditions of a frequency of 1 Hz, a dynamic force of 100 mN with a temperature range of −65–100°C and a heating rate of 5°C/min, were appropriate to evaluate the Tg. The tests were carried out in triplicate.

2.4. Evaluation of the digestibility of films

This was carried out in batch fermenters as described by Siew et al. [40]. The conditions used were those used at the Dunn Institute of Nutrition for food digestibility studies. Control experiments involved buffer in place of the faecal slurry.

3. Results and discussion

3.1. MFFT

The values for the MFFT of the films tested are presented in Table 1. The film prepared from Surelease alone had a value greater than 32°C. Hence, it would be expected to require spraying at temperatures of at least 42°C. The MFFT of the amylose itself was found to be <7.5°C and therefore, amylose would clearly be able to form films below 37°C, but the digestibility in the colon and ability to prevent drug release from formulations in the upper GI tract is not known. As the ethylcellulose and amylose are mixed in a range of solids ratios, just using the Surelease product as supplied could be possible at high amylose

Table 1
The minimum film forming temperatures (MFFT) of mixed dispersions[a]

Ethylcellulose: amylose ratio	Additional plasticiser (%W/W)	MFFT °C		
		T_1	T_2	T_{av}
1:0	0	>31.8	> 32.3	>32.1
3:1	0	<12.0	13.7	12.9
5:1	0	24.7	20.7	22.7
7:1	0	27.7	26.3	27.0
1:0	4	24.2	22.6	23.6
3:1	4	<12.1	<12.1	<12.1
5:1	4	<12.1	<12.1	<12.1
7:1	4	<12.1	<12.1	<12.1
1:0	8	15.3	15.6	15.5
3:1	8	<9.5	<9.5	<9.5
5:1	8	<9.5	<9.5	<9.5
7:1	8	<9.5	<9.5	<9.5
1:0	12	13.9	14.0	14.0
3:1	12	<8.0	<8.0	<8.0
5:1	12	<8.0	<8.0	<8.0
7:1	12	<8.0	<8.0	<8.0
0:1	0	<7.5	<7.5	<7.5

[a] T_1 and T_2, are duplicate measures and T_{av} is the average value.

contents, although at low amylose contents, a MFFT of 27°C may be marginally effective. The addition of the extra 4% of dibutyl sebacate reduces the value of the MFFT to a value below 12.1°C. Hence, all the ratios of ethylcellulose to amylose should be capable of forming a coat at temperatures below 37°C. Increasing the extra dibutyl sebacate to levels of 8 and 12% should also ensure that coating could be undertaken below 37°C but again such a coat may not be digestible by the bacterial enzymes. Therefore the properties of films containing 4% dibutyl sebacate were studied further.

3.2. DMA evaluation

Initial experiments were undertaken to establish that there was linearity in the stress/strain scans, i.e. measurements are being made in the linear elastic region. The films containing an extra 4% of DBS show a complex tan δ (the ratio of the loss to storage modulus) profile (Fig. 2a). There are three peaks recorded at −37.7, 0 and 50°C. Only the peak at 50°C was accompanied with a sudden drop in storage modulus and was therefore considered to be the α transition, representing the glass transition temperature Tg. The other peaks were considered to be secondary transition of band γ in decreasing order of temperature appearance. This value approximates to the Tg values previously reported for Surelease without additional plasticiser [41]. Curves for amylose alone show one tan δ peak at −25°C with a rapidly increasing tan δ above 25°C (Fig. 2b). There was little change in the value of the storage modulus at −25°C and when the position of the probe was considered, a sharp drop in probe height was noted. This suggests that the sample had shrunk. The tan δ at −25°C was unlikely to correspond to the Tg of amylose due to the lack of change in the storage modulus. This peak is most likely to be due to localised motions in the main chains. This is in good agreement with previously reported results, which suggested that the value for the Tg of amylose was most likely to be above its thermal decomposition temperature [42,43]. The position of the secondary relaxation peak would depend on the water content of the amylose film and has been reported to be between −85 and −25°C for amylose films formed from DMSO/water dispersions [42]. The second broad rise in tan δ at about 25°C was most likely due to water loss, which will be accompanied with stiffening and shortening of the sample.

The results for different ratios of Surelease and amylose

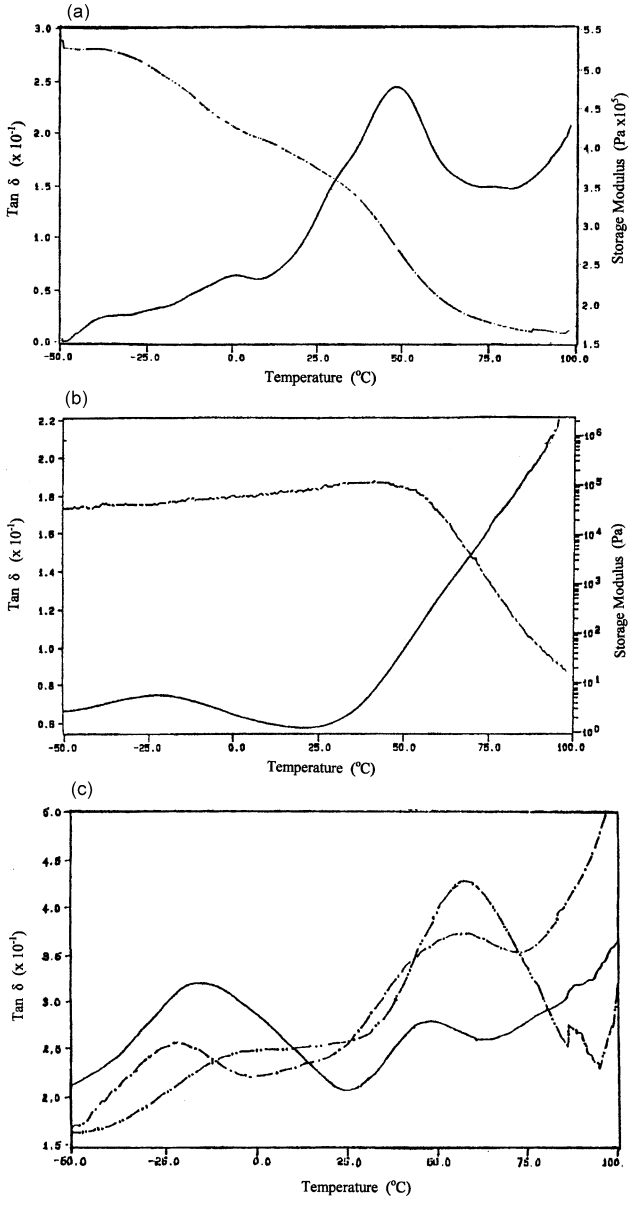

Fig. 2. DMA temperature time scans for: (a) Surelease and 4% DBS film; (b) amylose film; and (c) Surelease/amylose and 4% DBS mixed films: — Surelease 3 amylose 1; – – – Surelease 5 amylose 1; and –·–·– Surelease 7 amylose 1.

when an extra 4% DBS is added, are presented in Fig. 2c. There are two prominent tan δ peaks at approximately −20 and 55°C for the 3:1 and 5:1 ratios. The peak height at −20°C decreased relative to that at 55°C as the ratio of Surelease to amylose increased. This peak at −20°C disappeared altogether as the Surelease to amylose ratio increased to 7:1. The tan δ temperature profile for this ratio consisted of a tan δ peak at approximately 55°C with a shoulder at 0°C. The peaks at −20°C were most likely to be due to the secondary loss transition of the amylose component in the mixed film. The peaks at 0 and 55°C were most likely to be due to the β and α loss transitions of Surelease. Within limits of experimental error, the temperatures at which these peaks appeared in the mixed film correlated very well to the temperatures of the individual components. This suggests that, the main chain components of the Surelease and the amylose are immiscible. However, it is not clear if there was some degree of miscibility between the side chains of the ethylcellulose and the amylose. The disappearance of the β and γ peaks of Surelease (i.e. at 0 and −37.5°C, respectively) from the tan δ temperature curve of the mixed polymer film could be due to the 'overlay' effect of the tan δ peak from the amylose or it could be due to the shift of these secondary peaks as a result of partial miscibility of the side chains. In general the results confirm that amylose and ethylcellulose are not miscible, hence the amylose should be available for digestion.

3.3. Digestibility of mixed polymer films

The ability of the films to be digested under the conditions, which exist in the colon are fundamental to the whole concept of the system. Even if a film can be formed at temperatures below 37°C, if the bacterial enzymes present in the colon cannot digest the film, it will not provide a colon specific coating. The use of a controlled faecal slurry system used in food digestibility studies, has been described previously as a method of testing free films [40].

The result for the % of film weight lost after 24 h incubation for mixed films containing the additional 4% of dibutyl sebacate are shown in Fig. 3. The % of weight lost is clearly related to the initial content of the amylose film and that the slope of the line is close to unity suggests that the loss in weight is associated with the loss of amylose from the film. For equivalent films incubated under control conditions, the weight loss was never more than 5%. Films prepared from amylose alone, lost 43% of their weight in 6 h and 100% in 24 h. Under control conditions, these films did not lose any weight.

4. Conclusions

The addition of further quantities of the plasticiser already present in Surelease was found to lower the minimum film forming temperature and when mixed with a dispersion of amylose, the values of the minimum film forming temperature were such that it would be possible to spray into a fluid bed coater operating at temperatures below 37°C. Measurements of the glass transition temperature of ethylcellulose dispersions, to which a 4% additional level of plasticiser had been added prior to mixing with the amylose, by DMTA indicated that the two polymers were immiscible. Such findings indicate that the amylose is present in the film in domains, which are accessible to the bacterial enzymes for digestion. When mixed films were assessed for digestibility by use of a faecal slurry test, the presence of 4% additional plasticiser was found not to inhibit digestion. Hence such films have the potential to function as colon specific coating systems and can be applied from dispersions prepared and applied at temperatures below 37°C, which extends the range of systems which can be coated by amylose/ethylcellulose dispersions previously reported [1–3].

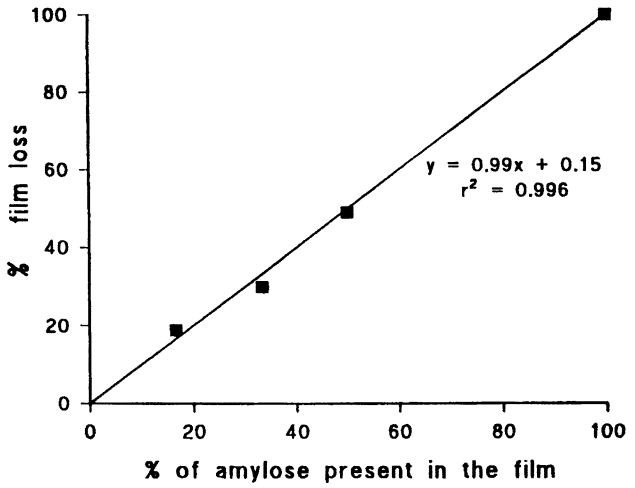

Fig. 3. The percentage of film left digested after 24 h of incubation in faecal slurry as a function of the percentage of amylose present in the Surelease/amylose mixed films containing additional 4% dibutyl sebacate.

Acknowledgements

Miss C.W. Leong wishes to thank the Overseas Research Students Award Scheme for financial support.

References

[1] S. Milojevic, J.M. Newton, J.H. Cummings, G.R. Gibson, R.L. Botham, S.G. Ring, M. Stockham, M.C. Allwood, Amylose as a coating for drug delivery to the colon; preparation and in vitro evaluation using 5-aminosalicylate pellets, J. Controlled Release 38 (1996) 75–84.

[2] S. Milojevic, J.M. Newton, J.H. Cummings, G.R. Gibson, R.L. Botham, S.G. Ring, M. Stockham, M.C. Allwood, Amylose as a coating for drug delivery to the colon; preparation and in vitro evaluation of glucose pellets, J. Controlled Release 38 (1996) 85–94.

[3] J.H. Cummings, S. Milojevic, M. Harding, W.A. Coward, G.R.

Gibson, R.L. Botham, S.G. Ring, E.P. Waright, M.A. Stockham, M.C. Allwood, J.M. Newton, In vivo studies of amylose – and ethylcellulose-coated [13C] glucose microspheres as a model for drug delivery to the colon, J. Controlled Release 40 (1996) 123–131.
[4] G.S. Rekhi, S.S. Jambhekar, Ethylcellulose. A polymer review, Drug Dev. Ind. Pharm. 21 (1995) 61–77.
[5] A. Onions, Films from aqueous based colloidal dispersions, Manuf. Chem. 57 (3) (1986) 55–59.
[6] D.P. Sheetz, Formation of films by drying latex, J. Appl. Polym. Sci. 9 (1965) 3759–3773.
[7] J.W. Van der Hoff, E.B. Bradford, W.K. Corrington, Transport of water through latex films, J. Polym. Sci. 41 (1973) 155–174.
[8] C. Bindschaedler, R. Gurney, E. Doelker, N.A. Peppas, Thermodynamics of swelling of polymer latex particles by a water-soluble solvent. 1 Theoretical considerations, J. Coll. Int. Sci. 108 (1985) 75–85.
[9] F.W. Goodhart, M.R. Harris, K.S. Murthy, R.U. Nesbitt, An evaluation of aqueous film forming dispersions for controlled release, Pharm. Technol. 8 (4) (1984) 64–71.
[10] A. Onions, Films from water-based colloidal dispersions, Manuf. Chem. 57 (4) (1986) 66–67.
[11] D. Hutchings, B. Kuzmak, A. Sakr, Processing considerations for an EC latex coating system: influence of curing time and temperature, Pharm. Res. 11 (1994) 1474–1478.
[12] J.W. Nicholson, Waterborne coatings, OCCA Monograph No. 8, Oil. Col. Chem. Assoc., Wembley, UK, 1994.
[13] J.W. Nicholson, Film formation by emulsion paints, Waterborne Coatings 12 (1989) 475–477.
[14] A. Laicher, C.A. Lorck, P.C. Gruenberg, H. Klemm, F. Stanislaus, Aqueous coating of pellets to sustained release dosage forms in a fluid-bed coater. Influence of product temperature and polymer concentration on in vitro release, Drugs Made Germany 38 (1995) 531–536.
[15] S.T. Yang, I. Ghebre-Sellasie, The effect of product bed temperature on the microstructure of Aquacoat-based controlled release coatings, Int. J. Pharm. 60 (1990) 109–124.
[16] N.H. Parikh, S.G. Porter, B.D. Robera, Aqueous dispersions of ethylcellulose. 1. Evaluation of coating process variables, Pharm. Res. 10 (1993) 525–534.
[17] A. Laicher, C.A. Lorck, P.C. Grunenberg, H. Klemm, F. Stanislaus, Aqueous coating of pellets to sustained-release dosage forms in a fluid bed coater. Influence of product temperature and polymer concentration on in vitro release, Pharm. Ind. 55 (1993) 1113–1116.
[18] W. Banks, C.T. Greenwood, Starch and its Components, The University Press, Edinburgh, 1975.
[19] R.C. Whistler, E.F. Paschall, J.N. BeMiller, Starch Chemistry and Technology, Academic Press, New York, 1984.
[20] J.A. Cura, P. Jansson, C.R. Krisman, Amylose is not strictly linear, Starch/Stärke 47 (1995) 207–209.
[21] C.G. Biliaderis, The structure and interactions of starch with food constituents, Can. J. Physiol. Pharmacol. 69 (1991) 60–78.
[22] G.K. Adkins, C.T. Greenwood, The isolation of cereal starches in the laboratory, Starch/Stärke 18 (1966) 213–218.
[23] H.S. Ellis, S.G. Ring, Study on some factors influencing amylose gelation, Carbohydr. Polym. 5 (1985) 201–213.
[24] M.A. Whittam, P.D. Orford, S.G. Ring, S.A. Clark, M.L. Parker, P. Cairns, M.J. Miles, Aqueous dissolution of crystalline and amorphous amylose-alcohol complexes, Int. J. Biol. Macromol. 11 (1989) 339–344.
[25] I.A. Wolff, H.A. Davis, J.E. Cluskey, L.J. Grundrun, C.E. Rist, Preparation of films from amylose, Ind. Eng. Chem. 43 (1951) 915–919.
[26] M.J. Miles, V.J. Morris, S.G. Ring, Some recent observations on the retrogradation of amylose, Carbohydr. Polym. 4 (1984) 73–77.
[27] M.J. Miles, V.J. Morris, S.G. Ring, The roles of amylose and amylopectin in gelation and retrogradation of starch, Carbohydr. Res. 135 (1985) 257–269.
[28] J.J. Muller, C. Gernet, W. Schulz, E. Muller, W. Vorweg, G. Damaschun, Computer simulations of X-ray scattering curves; gelation and crystallisation process in amylose solutions, Biopolymers 35 (1995) 271–288.
[29] H.N. Englyst, J.H. Cummings, Resistant starch, a 'new' food component: a classification of starch for nutritional purposes, in: I.D. Morton (Ed.), Cereals in a European Context. First European Conference on Food Science and Technology, Ellis Horwood, Chichester, UK, 1987, pp. 221–233.
[30] S.G. Ring, J.M. Gee, M. Whittam, P.D. Orford, I.T. Johnson, Resistant starch: its chemical form in foodstuff and effect on digestibility in vitro, Food Chem. 28 (1988) 97–109.
[31] V.M. Leloup, P. Colonna, S.G. Ring, K. Roberts, B. Wells, Microstructure of amylose gels, Carbohydr. Polym. 18 (1992) 189–197.
[32] H.N. Englyst, S.M. Kingman, J.H. Cummings, Classification and measurement of the nutritionally important starch fractions, Eur. J. Clin. Nutr. 46 (Suppl. 2) (1992) S33–S50.
[33] S.G. Ring, Stiff tests for designer starches, Chem. Br. 31 (1995) 303–307.
[34] P. Cairns, L. Sun, V.J. Morris, S.G. Ring, Physicochemical studies using amylose as an in vitro model for resistant starch, J. Cereal Sci. 21 (1995) 37–47.
[35] V.M. Leloup, P. Colonna, S.G. Ring, Physicochemical aspects of resistant starch, J. Cereal Sci. 16 (1992) 253–266.
[36] H.N. Englyst, G.T. Macfarlane, Breakdown of resistant and readily digestible starch by human gut bacteria, J. Sci. Food Agric. 37 (1986) 699–706.
[37] G.T. Macfarlane, H.N. Englyst, Starch utilisation by the human large intestine, Lett. Appl. Microbial. 60 (1986) 195–201.
[38] G.T. Macfarlane, G.R. Gibson, J.H. Cummings, Extra cellular and cell-associated glycosidase activities in different regions of the human large intestine, Lett. Appl. Microbiol. 12 (1991) 3–7.
[39] G.T. Macfarlane, G.R. Gibson, J.H. Cummings, Comparison of fermentation reactions in the different regions of the human colon, J. Appl. Bact. 72 (1992) 57–64.
[40] L.F. Siew, A.W. Basit, J.M. Newton, The properties of amylose-ethylcellulose films cast from organic-based solvents as potential coatings for colonic drug delivery, Eur. J. Pharm. Sci. 11 (2000) 133–139.
[41] U. Iyer, W. Hong, N. Das, I. Ghebre-Sellassie, Comparative evaluation of three organic solvent and dispersion-based ethylcellulose coating formulations, Pharm. Technol. 9 (1990) 68–86.
[42] M. Scandola, G. Ceccorulli, M. Pizzoli, Molecular motions of polysaccharides in the solid state: dextrin, pullulan and amylose, Int. J. Biol. Macromol. 13 (1991) 254–260.
[43] P.D. Orford, R. Parker, S.G. Ring, A.C. Smith, Effect of water as a diluent on the glass transition behaviour of malto-oligosaccharides, amylose and amylopectin, Int. J. Biol. Macromol. 11 (1989) 91–96.