

Characterization of moisture interactions in some aqueous-based tablet film coating formulations*

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Three methods—radiotracer, differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)—have been employed to evaluate moisture interactions in aqueous-based hydroxypropyl methylcellulose films containing polyethylene glycol 400, polyethylene glycol 1000 or polyvinyl alcohol. The radiotracer employed was tritiated water. Using a proposed classification, the water present in the films was placed in three categories: tightly bound, moderately bound and free. The tightly bound water in hydroxypropyl methylcellulose and hydroxypropyl methylcellulose/polyvinyl alcohol films was related to the crystallinity of the films whilst tightly bound water was practically non-existent in the plasticized systems thus indicating the absence of crystallinity. Free (or freezable) water could not be detected in the films using DSC. The moisture content data obtained by TGA were considered to represent moderately bound water. The moderately bound water content of the film systems was in the rank order of the hydrophilicity of the polymer additives: polyethylene glycol 400 > polyethylene glycol 1000 > polyvinyl alcohol. This order was reversed for the calculated free water content.

The solvent or solvent system employed in film coatings usually plays a considerable role in determining film morphology, and retained solvent exerts important effects on film properties (Funke & Zorll 1971). Funke (1973/4) has observed that residual solvent plasticizes films while Runt & Rim (1982) showed that film thickness, blend preparation temperature, solvent evaporation rate and the type of solvent used were some of the factors which affected the development of crystallinity in poly (*N*-caprolactone) when this polymer was blended with poly(styrene-co-acrylonitrile). Hassel (1976) also reported that water in polymers often influenced tensile strength, mechanical modulus, surface adhesion, polymer hydrolysis, bubble formation and processing time.

Solvent retention in pharmaceutical film coatings has, however, received virtually no attention by researchers although some workers have recognized that solvent and environmental moisture usually affected film properties. Nadkarni et al (1975) observed that film adhesion to tablets was promoted when the solubility parameter of a coating solvent was close to that of the polymer. Fung & Parrott (1980), using water and some organic solvent systems, found that the adhesion of hydroxypropyl

methylcellulose film was lowest for films cast from aqueous systems. Aulton et al (1981) reported that environmental moisture has a plasticizing influence on hydroxypropyl methylcellulose films; the higher the humidity of the environment the lower the tensile strength and Young's modulus of the films.

Much effort has been made by polymer science investigators to categorize water in polymers, particularly cellulose. Some of the techniques used include calorimetry (Magne et al 1947; Davies & Webb 1969; Nelson 1977; Bair 1981), coulometry (Hassel 1976; Bair 1981), desorption (Boeson 1970), infrared spectroscopy (Malcolm 1970) and nuclear magnetic resonance (Ogiwara et al 1969; Carles & Scallan 1973; Froix & Nelson 1975). Various terms such as 'bound', 'tightly bound', 'highly bound', 'primary bound', 'secondary bound', 'loosely bound', 'capillary', 'non-solvent', 'free' and 'freezable' have been used by these and other researchers to describe the different forms of water found in polymers. The large number of descriptive terms reflects the lack of complete agreement on the nature of the moisture in polymers. This is also indicated by the disparity of the results obtained even for identical polymers; one of the main reasons for this is the variety of methods employed.

The increasing use of water as a solvent in film coating formulations in the pharmaceutical industry, as well as the adverse effect of environmental moisture on films, have emphasized the need to examine and characterize moisture in film coatings.

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The evaluation of moisture interactions in hydroxypropyl methylcellulose films containing polyvinyl alcohol, polyethylene glycol 400 or polyethylene glycol 1000, cast from aqueous systems, is presented in this paper. Three methods were employed: (i) a radiotracer technique, involving the use of tritiated water ($^3\text{H}_2\text{O}$), (ii) differential scanning calorimetry (DSC), and (iii) thermogravimetric analysis (TGA). The radiotracer technique, used apparently for the first time in this study to characterize the various forms of moisture in polymers, is simple and very precise. The small amounts required and its low radiation energy obviate the need for elaborate protection.

MATERIALS AND METHODS

Hydroxypropyl methylcellulose (Pharmacoat 606) and polyvinyl alcohol (Poval PA-5)—with a degree of hydrolysis of 88%—were manufactured by Shin-Etsu Chemical Co. Ltd, Japan. Polyethylene glycols 400 and 1000 were supplied by BDH Chemicals Ltd, Poole, UK, while the tritiated water (5 mCi ml^{-1}) was obtained from Amersham International Ltd, Amersham, UK. Insta-gel (Packard Instrument Co., Inc., Illinois, USA), a xylene-based cocktail, was used as the scintillant.

Film formulations were prepared from 10% w/w aqueous solutions of the polymers and the films were cast using the rotating cylinder technique described in a previous study (Okhamafe & York 1983). Tritiated water was incorporated in the formulations for radiotracer studies to produce a specific activity of $5\ \mu\text{Ci ml}^{-1}$, prior to casting. The cylinder substrate employed in this case, however, was much shorter because only 30 ml of the formulation was cast.

Radiotracer technique

For each prepared film, moisture content was evaluated in the following three ways: (i) just after casting, (ii) after equilibration in a desiccator over a saturated solution of sodium chloride (75% rh) for one week, and (iii) after conditioning under vacuum over phosphorous pentoxide (P_2O_5) for one week. Preliminary studies indicated that the moisture content of the films reached an equilibrium state within three days when stored in a desiccator at 75% rh. Six film specimens were employed in each test. About 75 mg of film specimen, accurately weighed, was dissolved in 0.5 ml of distilled water in a glass vial and then dispersed in 10 ml of the scintillation cocktail. Measurement of the emitted beta radiation was carried out in an automatic Packard Tri-Carb

Table 1. Moisture content (\pm standard deviation) of hydroxypropyl methylcellulose (HPMC) films containing polyethylene glycols 400 and 100, and polyvinyl alcohol (PVA) just after casting.

Content of polymer additive (wt%)	Moisture content (%)		
	HPMC/PEG 400	HPMC/PEG 1000	HPMC/PVA
0	1.79 \pm 0.09	1.79 \pm 0.09	1.79 \pm 0.09
5	0.57 \pm 0.04	0.46 \pm 0.05	
10	0.49 \pm 0.02	0.47 \pm 0.05	2.28 \pm 0.13
15	0.44 \pm 0.03	0.51 \pm 0.04	
20	0.40 \pm 0.02	0.49 \pm 0.03	2.37 \pm 0.10
25	0.47 \pm 0.02	0.50 \pm 0.04	
30	0.47 \pm 0.03	0.46 \pm 0.05	2.33 \pm 0.14
40			2.35 \pm 0.14
50			2.44 \pm 0.20
60			2.58 \pm 0.28

Table 2. Moisture content (\pm standard deviation) of hydroxypropyl methylcellulose (HPMC) films containing polyethylene glycols 400 and 100 (PEG 400 and 1000), and polyvinyl alcohol (PVA) after conditioning for one week at 75% rh, 25 $^\circ\text{C}$ in desiccator.

Content of polymer additives (wt%)	Moisture content (%)		
	HPMC/PEG 400	HPMC/PEG 1000	HPMC/PVA
0	10.93 \pm 0.25	10.93 \pm 0.25	10.93 \pm 0.25
5	10.43 \pm 0.15	11.00 \pm 0.38	
10	10.44 \pm 0.13	11.21 \pm 0.17	12.93 \pm 0.24
15	10.79 \pm 0.18	11.37 \pm 0.20	
20	11.55 \pm 0.26	11.49 \pm 0.23	13.64 \pm 0.20
25	12.65 \pm 0.31	11.94 \pm 0.21	
30	13.59 \pm 0.38	12.41 \pm 0.24	14.28 \pm 0.21
40			14.66 \pm 0.26
50			15.13 \pm 0.30
60			15.97 \pm 0.43

460C spectrometer using a counting time of 10 min. This counting time produced counts of sufficiently high precision. 2σ (where σ is standard deviation) was 0.21–0.93%, $<0.2\%$ and 0.23–3.0%, respectively, for films examined just after casting, after equilibration at 75% rh for one week, and after storage under vacuum over P_2O_5 for one week. Quenching of beta radiation by the polymers was less than 3% and the results were corrected accordingly.

Differential scanning calorimetry

Film specimens (each consisting of film discs of 5 mm diameter) were equilibrated at 25 $^\circ\text{C}$, 75% rh in a desiccator over a saturated solution of sodium chloride for one week. About 20 mg specimen, accurately weighed, was placed in a crimped aluminium sample pan with a pierced lid and quenched in a DuPont 1090/910 differential scanning calorimeter (DSC) to $-100\ ^\circ\text{C}$ using liquid nitrogen.

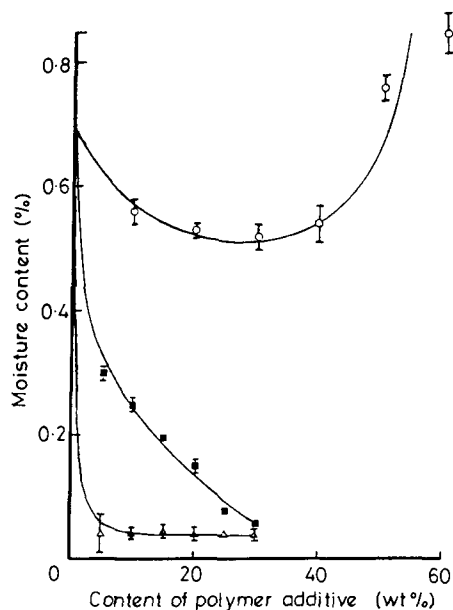


Fig. 1. Moisture contents of hydroxypropyl methylcellulose films containing polyethylene glycols 400 (■) and 1000 (△), and polyvinyl alcohol (○) after conditioning for one week under vacuum over phosphorus pentoxide at 25 °C.

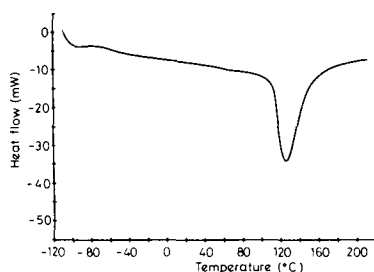


Fig. 2. Differential scanning calorimeter thermogram for hydroxypropyl methylcellulose film containing 25 wt% of polyethylene glycol 400.

It was held isothermally at this temperature for 5 min and then program heated to 200 °C at a rate of 10 °C min⁻¹ under a nitrogen gas atmosphere. Thermograms were examined for endotherms around 0 °C indicating melting of water.

Thermogravimetric analysis (TGA)

Disc samples (about 20 mg) of the films examined above were placed in the aluminium sample holder of a DuPont 1090/951 thermogravimetric analyser (TGA) which incorporates a microbalance with a sensitivity of $\pm 1 \times 10^{-2}$ mg. Moist air at 75% rh was

let into the balance at a rate of 30 ml min⁻¹ from a controlled humidity line incorporating a digital hygrometer (model SHA-D, Shaw Meters, Bradford, UK) and a flow meter until the film attained equilibrium weight at 25 °C. The moist air was then shut off, and simultaneously, program heating at 10 °C min⁻¹ was initiated under nitrogen gas purge (10 ml min⁻¹). Thermograms were obtained between 25 and 300 °C. Moisture loss as well as the temperature range over which moisture was evolved were calculated with the aid of a DuPont 1090 TGA data analysis program.

RESULTS AND DISCUSSION

Radioisotope technique

Tables 1 and 2 as well as Fig. 1 show the moisture content data under the three different test conditions. Just after casting (Table 1), the moisture contents of the hydroxypropyl methylcellulose films plasticized with the polyethylene glycols were lower than that of the unplasticized film. Practically all the reduction in residual moisture was achieved at the lowest plasticizer concentration used (5 wt% based on the content of the film former). The effects of the two plasticizers were identical in magnitude. On the other hand, the levels of retained water in hydroxypropyl methylcellulose/polyvinyl alcohol blends just after casting were generally higher than that of hydroxypropyl methylcellulose alone.

Table 2 indicates that when equilibrated at 75% rh, the moisture content of hydroxypropyl methylcellulose/polyvinyl alcohol blend was higher than that of the film-former alone; the higher the content of polyvinyl alcohol, the higher the moisture content of the blend. Although the system containing polyethylene glycol 1000 showed a similar trend, the effect was less pronounced. After an initial fall in the moisture content of the films plasticized with polyethylene glycol 400, moisture levels rose rapidly when the plasticizer concentration reached 20 wt%.

When the films were stored under vacuum over P₂O₅, the moisture content of hydroxypropyl methylcellulose fell in the presence of the plasticizers (see Fig. 1). Maximum reduction in water content was attained at a plasticizer concentration of 5 wt% for the system containing polyethylene glycol 1000 but for hydroxypropyl methylcellulose/polyethylene glycol 400 films, moisture content decreased steadily with increase in plasticizer level. The residual solvent of hydroxypropyl methylcellulose film was initially lowered in the presence of polyvinyl alcohol but this was followed by an increase when the level of the polymer additive exceeded 40 wt%.

Differential scanning calorimetry

Fig. 2 shows the thermogram for hydroxypropyl methylcellulose film plasticized with 25 wt% of polyethylene glycol 400 and was typical for all the other films assessed. The endothermic peak between 85 and 180 °C is due to the loss of water, by vaporization, from the film. The wide temperature range covered by the peak suggests that moisture loss was slow, presumably because the water was hydrogen bonded to the hydroxyl groups on the polymers. Thus, in addition to the latent heat of vaporization, energy is required to sever the links between water and the polymers. For this reason, the area of the endothermic peak does not provide an acceptable estimate of the evolved moisture. Although a number of researchers (e.g. Magne et al 1947; Nelson 1977; Baker & Cattiaux*) using calorimetric techniques have reported the presence of freezable water in some polymers, it is apparent from the thermogram in Fig. 2 that freezable water was not indicated since the melting endotherm for frozen water was absent. The water evolved at elevated temperatures was bound to the polymer matrix and therefore did not behave like bulk water. Hence it was incapable of freezing or melting.

However, there is reason to believe that at the storage humidity (75% rh) freezable water might have been present in the films because a fine mist, resembling condensed moisture, was observable, especially on the plasticized films. Usually, the fine mist disappeared when the film was left in the laboratory environment for 2 min. This moisture was probably lost at the lower humidity of the laboratory during the manipulative process of preparing the samples for DSC measurements and this difficulty could not be overcome.

Thermogravimetric analysis (TGA)

The TGA thermograms obtained for all the films were generally similar to those shown in Fig. 3. This indicates a transition, equivalent to about 10% weight loss by the sample, in the 30 to 130 °C temperature range. A sharper transition, beginning at about 260 °C, led to a loss of about 70 wt% of the original film sample. The first transition was considered as indicating loss of moisture from the film while the second transition represented film decomposition. Any moisture remaining in the film after the first transition would be lost during the second transition. The moisture content results, based on

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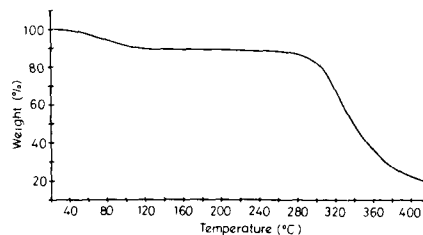


FIG. 3. Thermogravimetric analyser thermogram for polyvinyl alcohol film.

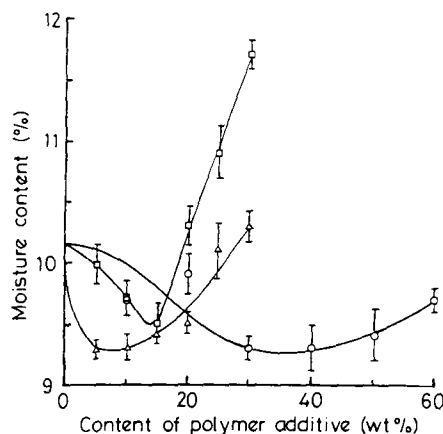


FIG. 4. Moderately bound water contents of hydroxypropyl methylcellulose films containing polyethylene glycols 400 (□) and 1000 (Δ), and polyvinyl alcohol (○) at 75% rh, 25 °C.

Table 3. Moisture transition spread (\pm mean deviation) of hydroxypropyl methylcellulose (HPMC) films containing polyethylene glycols 400 and 100 (PEG 400 and 1000), and polyvinyl alcohol (PVA).

Content of polymer additive (wt%)	Moisture transition spread (°C)		
	HPMC/PEG 400	HPMC/PEG 1000	HPMC/PVA
0	38.6 \pm 0.9	38.6 \pm 0.9	38.6 \pm 0.9
5	39.2 \pm 1.3	40.2 \pm 0.9	
10	39.3 \pm 1.0	37.0 \pm 1.4	42.4 \pm 2.5
15	38.0 \pm 1.7	38.9 \pm 1.0	
20	40.5 \pm 1.6	40.9 \pm 1.9	52.1 \pm 1.1
25	38.1 \pm 2.3	38.7 \pm 1.8	
30	40.4 \pm 2.1	29.6 \pm 2.0	51.5 \pm 2.0
40			49.2 \pm 1.8
50			53.3 \pm 1.7
60			52.4 \pm 2.3
PVA alone			51.4 \pm 1.5

the first transition, are plotted against additive concentration in Fig. 4. The data are termed 'moderately bound' moisture as is explained later in the discussion. The moisture level of hydroxypropyl methylcellulose film fell initially when a polymer

additive was incorporated but increased as the content of the additive was further raised. This effect was more pronounced for the polymer system plasticized with polyethylene glycol 400.

The moisture transition spread (i.e. the temperature range covered by moisture transition) data are recorded in Table 3. The values for the plasticized and unplasticized systems are identical but are smaller than those of hydroxypropyl methylcellulose/polyvinyl alcohol and polyvinyl alcohol films, respectively. Moisture transition spread indicates the ease with which moisture is lost from the films. The rate of moisture loss depends primarily on the strength of the water-polymer link and the extent to which the passage of water molecules out of the film is physically hindered by the structure of the polymers. However, all three polymer additives are structurally linear and consequently their capacities to hinder moisture escape from the films are likely to be similar. Therefore, the greater moisture transition spreads of the polyvinyl alcohol systems are probably due to stronger water-polyvinyl alcohol interaction.

Unlike the films stored in a desiccator at 75% rh, those exposed to a steady stream of moist air at the same humidity did not have fine mists of condensed moisture on their surfaces. The implication, therefore, is that at the humidity employed in this investigation, unbound (and hence freezable) water could probably be found in close contact with the films under static conditions such as obtained in a desiccator but this form of water could not exist on the films at the same humidity presented under dynamic conditions. This observation is supported by the quantitative difference between the TGA and radiotracer data as well as the fact (see Fig. 3) that substantial moisture loss by the film samples did not begin until the test temperature reached 40 °C.

Moisture interactions

Based, in part, on a classification employed by Magne et al (1947) for water in cellulose (hydroxypropyl methylcellulose is a cellulose ether), water exists in three principal forms in the films examined in the present study.

(a) Water bound within the crystalline phase. As the film dries, some portions may become structurally well-ordered, thus producing a crystalline phase and the fraction of solvent involved in the crystallization process is trapped within the phase. Since this phase is inaccessible, the trapped solvent will usually only be lost when the crystalline phase is degraded, e.g. by thermal or chemical means. The water can

Table 4. Moisture content data (%) for PVA film at 25 °C.

	Moisture content (%)
Just after casting	9.65 ± 0.28 ^a
Stored at 75% rh in a desiccator for one week	23.24 ± 0.51 ^a
Tightly bound water	7.84 ± 0.12 ^a
Moderately bound water	10.10 ± 0.4 ^b
Free water	5.30

^a Standard deviation.

^b Mean deviation.

therefore be appropriately described as 'tightly bound' water.

(b) Water adsorbed to hydroxyl groups in the amorphous (non-crystalline) phase of the film mainly by hydrogen bonding. Some of these hydroxyl groups were previously free while others are made available when water severs the hydrogen bonds between adjacent polymer segments, especially when environmental humidity is high. This water is plasticizing the film because by interacting with hydroxyl groups, it opens up the film structure (swelling) and increases segmental mobility. Since the adsorption process can be relatively easily reversed without destroying the film, this form of water may be termed 'moderately bound' water.

(c) When all hydroxyl groups in the amorphous phase have been satisfied, and depending on the nature of the polymeric film and the humidity of the environment, water may be found in a bulk or condensed form on the film surface or within voids or other defects that exist in the film. Unlike the other two types, this water behaves like bulk water because it is capable of freezing. The term 'free' water is used for this form of water.

The moisture content data in Fig. 1 can be considered to represent tightly bound water because the intense extraction procedure used (under vacuum over P₂O₅ for one week) will have removed the other two forms of water. This observation is supported by the almost total absence of tightly bound water in the plasticized films. Plasticization decreases molecular order and therefore any tendency towards the formation of a crystalline phase. The relatively high tightly bound water content of hydroxypropyl methylcellulose/polyvinyl alcohol films is a reflection of the crystalline nature of polyvinyl alcohol, since as reported previously (Okhamafe & York 1985) hydroxypropyl methylcellulose lost its crystallinity when it was blended with polyvinyl alcohol. The tightly bound water content of 7.84% for PVA (see Table 4) is a third of

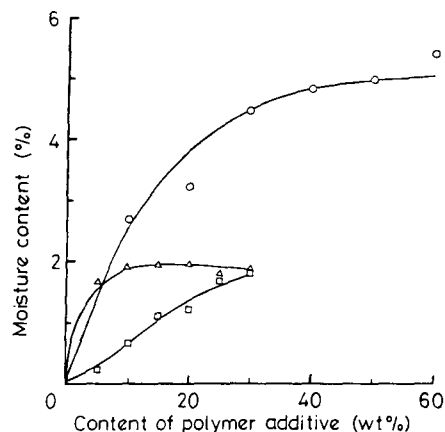


FIG. 5. Free water contents of hydroxypropyl methylcellulose films containing polyethylene glycols 400 (□) and 1000 (△), and polyvinyl alcohol (○) at 75% rh, 25°C.

its total water content at 75% rh (under static condition). Thus estimates of tightly bound water can serve as a useful indication of both plasticization and crystallinity.

It was proposed earlier that the moisture content data from TGA (Fig. 4) did not include free water. Apparently, the data also do not incorporate tightly bound moisture in view of the inaccessibility of the crystalline phase. The TGA data have therefore been considered as representing moderately bound moisture. It seems possible to estimate compatibility in polymer blends from moderately bound moisture data. Hydrogen bond interaction between hydroxypropyl methylcellulose and polymer additive would reduce the affinity of the blend for water which accounts for the initial decrease in moisture content with increase in the level of the polymer additive (see Fig. 4). As the additive concentration was further raised, a compatibility limit (corresponding to the moisture content minimum) was reached beyond which moisture content began to rise as a result of the free hydroxyl groups on the excess polymer additive. Thus the compatibility limits of the polymer additives in the blends are 10 wt% (polyethylene glycol 1000), 15 wt% (polyethylene glycol 400) and 40 wt% (polyvinyl alcohol), and may be compared with the 15, 20 and 40 wt%, respectively, obtained

from glass transition studies (Okhamafe & York 1985). Above the compatibility limit, the rate of increase of moderately bound moisture content was in the rank order of the hydrophilicity of the polymer additives: polyethylene glycol 400 > polyethylene glycol 1000 > polyvinyl alcohol.

The free moisture content, W_F , of the films was calculated from the following relation:

$$W_F = W_A - (W_M + W_T) \quad (1)$$

where W_A is the total moisture content at 75% rh (under static conditions), and W_M and W_T are the moderately bound and tightly bound water contents, respectively. The free moisture content is plotted against concentration of polymer additive in Fig. 5. The results indicate that the lower the moisture affinity (or hydrophilicity) of the polymer additives, the greater the unbound of free moisture contents of the films. The rank order is thus the reverse of that found for moderately bound water.

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