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Thermal Characterization of Drug/Polymer and Excipient/Polymer Interactions in Some Film Coating Formulation*

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Abstract—Some probable consequences of the dissolution/migration of a major solid dosage component in or into an applied film coating during or after a film coating operation have been investigated using free films of hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) incorporating small amounts of either lactose (a diluent) or ephedrine hydrochloride (a drug). Intrinsic features of the films such as softening, glass transition, crystallinity and melting were examined by differential scanning calorimetry and thermomechanical analysis. Generally, the results indicate that ephedrine hydrochloride exhibited plasticizing activity in both HPMC and PVA films. On the other hand, incorporation of lactose produced an opposite effect (stiffening) in PVA films as demonstrated by increased glass transition temperature and crystallinity. On the basis of these findings, it was proposed that the undesired presence of a component of a solid dosage core in the applied film coating could significantly alter its end-use properties such as diffusivity and the incidence of film coating defects. It was also shown that the application of the relationship of Moelter & Schweizer (1949) in the evaluation of the plasticizer efficiency of non-homologous additives could pose problems of interpretation.

There is increasing recognition that the bulk properties of film coatings are, to a major extent, dependent on their intrinsic characteristics. Most of the problems encountered in film coating practice, e.g., bridging of monograms, edge splitting, tackiness, poor film/tablet adhesion, are usually manifestations of coating behaviour at the molecular level. Therefore sound knowledge of, as well as the capacity to control, the intrinsic features of film coating materials such as glass transition temperature, softening and melting points, crystallinity, internal stress, intrinsic viscosity, and moisture interactions, would be of immense value to the formulation scientist engaged in coating systems design. This fundamental approach provides potentially the shortest route to the solution of various film coating problems.

The works of Aulton et al (1983) and Simpkin et al (1983) suggest that dissolution of a small amount of excipient or drug (contained in a solid dosage form) in a film coating during a coating operation, and/or migration of the excipient/drug into the applied coating over a period of time following the coating application, could occur in practice. Dissolution is particularly likely if the drug or excipient is soluble in the solvent used for the preparation of the coating formulation. The mode of migration could be by drug/excipient dissolution in the residual solvent of the coating or in the moisture adsorbed by the coating where the coated product has been exposed to a high humidity environment such as prevails in the tropics. Migration may also take place by a sublimation mechanism as previously noted for salicylic acid which is a degradation product of aspirin (Okhamafe & York 1986).

The undesired presence of a drug or an excipient in an applied film coating may substantially alter the mechanical adhesion and permeation characteristics of the coating. For example, Okhamafe & Igbinadolo (1988) observed that although the moisture diffusivity of a hydroxypropyl methylcellulose (HPMC) film was either lowered or unchanged in the presence of ephedrine hydrochloride or lactose, incorporation of these additives markedly enhanced the moisture diffusivity of polyvinyl alcohol (PVA) films. Thus it seems that the nature and degree of drug/polymer or excipient/polymer interactions may exert a significant influence on bulk film properties. In the present investigation, aqueous-based HPMC and PVA films containing small quantities of either lactose or ephedrine hydrochloride have been examined using differential scanning calorimetry (DSC) and thermomechanical analysis (TMA) in an attempt to acquire an insight into the nature and extent of interactions between the polymers and the additives.

Materials and Methods

Hydroxypropyl methylcellulose USP (Pharmacoat 606) and 88% hydrolysed polyvinyl alcohol (Poval PA-5) were manufactured by Shin-Etsu Chem. Co. Ltd., Tokyo, Japan. Ephedrine hydrochloride (BDH Chemicals Ltd., Poole, UK) and α-lactose monohydrate (Hopkins & Williams, Chadwell Health, UK) were the additives incorporated in the polymer films. Free films were cast from mixtures of 10% w/v solution of the polymers and 5% w/v solutions of the additives using a procedure described in an earlier study (Okhamafe & Iwebor 1986). Up to 5 and 10 wt% (based on polymer content) of lactose and ephedrine hydrochloride, respectively, were incorporated in the films.

The glass transition temperature and crystallinity of the films were determined with a Du Pont 1090/910 differential

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scanning calorimeter. In addition, softening and melting/decomposition points, as well as glass transition temperature, were obtained with a Perkin Elmer TMS-2 thermomechanical analyser. Details of the procedures used can be found elsewhere (Okhamafe & York 1988). At least duplicate measurements were made in all cases and mean deviation generally did not exceed 2°C.

Results and Discussion

In a recent study (Okhamafe & York 1988), we observed that the TMA thermograms of the polymers examined in the present work exhibited hitherto unknown thermal transitions at low temperatures (between 25 and 43°C) in addition to the well established high temperature transitions. The DSC thermograms also manifested the high temperature transitions but not the low temperature ones. Both the high and low temperature transitions were identified and interpreted as follows (Okhamafe & York 1988):

HPMC. The TMA penetration thermogram of this polymer demonstrated a low temperature softening point (Ts_1), another softening point (Ts_2) at a much higher temperature, and ultimately, a degradation point (Td). The TMA expansion thermogram exhibited two glass transition temperatures, Tg_1 and Tg_2, which were considered to correspond to Ts_1 and Ts_2, respectively. However, the DSC thermogram manifested only one glass transition temperature (Tg) which was believed to be equivalent to Ts_2 and Tg_2 on the TMA penetration and expansion thermograms, respectively.

PVA. The TMA penetration thermogram also indicated a low temperature softening (Ts_1) and a high temperature softening (Ts_2). In addition, a melting point (Tm) was identified. On the other hand, the TMA expansion thermogram clearly showed softening rather than expansion, and hence glass transition, in a conventional sense, could not be detected. However, the DSC thermogram displayed a glass transition temperature (Tg), believed to correspond to Ts_2, and a melting transition (endotherm) which provided estimates of melting point (Tm) and relative degree of film crystallinity.

Low temperature transitions

In our previous paper (Okhamafe & York 1988) the low temperature transition (Ts_1 and Tg_1) were thought to be low energy transitions since they were not manifested on the DSC thermograms. The transitions were attributed to the unwinding of the secondary and tertiary coiled structures of the polymers involving the rupture of the mainly weak (low energy) intra- and intermolecular bonds. We now believe, until further evidence is obtained, that these transitions may have their origin in the film casting procedure employed which resulted in unstable secondary and tertiary polymer film structures. Thus the transitions at Ts_1 and Tg_1 may not, in the classical sense, be considered as true softening and glass transitions, respectively, especially since they have so far only been observed in TMA thermograms.

Table 1 shows the effect of ephedrine hydrochloride and lactose on the low temperature transitions of HPMC and PVA films. The additives did not exert any clearly discernible influence on these transitions. This suggests, as previously discussed, that the forces responsible for the secondary and tertiary coiled structures of the polymers were essentially unaffected by the presence of the additives. The observation does not imply that the magnitude of these transition data would also be independent of other formulation and process variables. In view of the closeness of the transitions temperature to room and/or process temperatures, they definitely merit further study.

Table 1. Low temperature transition data (from TMA) for HPMC and PVA films containing ephedrine hydrochloride and lactose.

Content of additive	Ephedrine			Lactose		
	PVA	HPMC		PVA	HPMC	
(wt%)	Ts_1	Ts_1	Tg_1	Ts_1	Ts_1	Tg_1
0	32·1	40·7	31·0	32·1	40·7	31·0
1				31·8	41·2	32·0
2	30·5	37·6	31·5	30·9	38·7	32·1
3				32·0	39·1	31·5
4	32·2	36·9	33·1	31·2	38·4	32·9
5				29·6	41·3	33·5
6	29·0	39·4	31·2			
8	31·3	41·7	33·8			
10	29·8	38·7	34·2			

High temperature transitions

Glass transition. Fig. 1 shows the relationship between both the TMA and DSC glass transition temperature (Tg) of HPMC film and the amount of incorporated additive. It is interesting that although the TMA and DSC data, respectively, differ quantitatively, similar trends for each of the film systems studied were obtained. The results indicate that the Tg of HPMC was generally unaffected by the presence of lactose. Since visual observation did not reveal any signs of incompatibility, it can be said that there was complete lactose/HPMC miscibility over the additive concentration range examined. Usually, inclusion of relatively small molecules in polymers should bring about plasticization of the

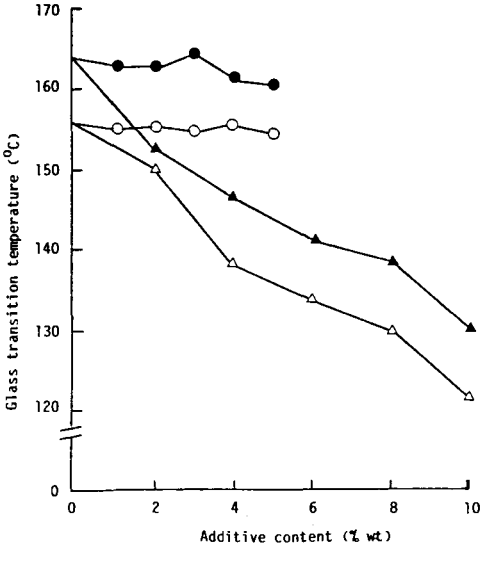

FIG. 1. Glass transition temperature of HPMC film containing lactose (○,●) and ephedrine hydrochloride (△,▲). Open symbols = DSC data, closed symbols = TMA data.

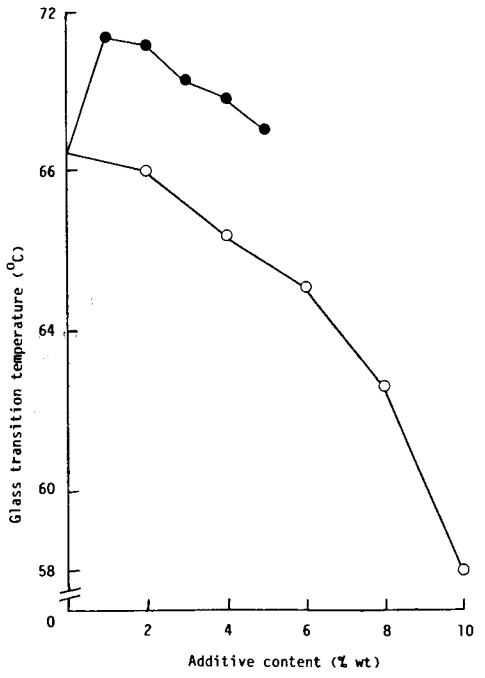

FIG. 2. Glass transition temperature of PVA film containing lactose (●) and ephedrine hydrochloride (○) and obtained by DSC.

latter as a result of an increase in the segmental mobility and free volume of the film. This situation, apparently did not occur in the lactose/HPMC system for two probable reasons. The polymer and the additive have basically the same molecular unit—anhydroglucose. Lactose has four hydroxyl groups per molecular unit and can therefore interact strongly and extensively with the polymer through a pervasive cross-linking network of hydrogen bonds. The result should therefore be a fall in polymer chain mobility and hence a rise in Tg. However, this ignores the probability that the mere physical presence of the additive molecules between adjacent polymer chains could exert an opposite effect, i.e. increased segmental mobility (plasticization) and thus a fall in Tg.

It would appear that over the lactose concentration range assessed, the two opposing phenomena were approximately balanced with the result that Tg remained essentially unchanged.

Fig. 1 also shows that the Tg of HPMC fell steadily as ephedrine hydrochloride content was increased. Since this additive has fewer hydrogen bonding groups (two per molecule) than lactose, the intensity of the cross-linking hydrogen bond network would be considerably less in the ephedrine hydrochloride/HPMC system. Hence plasticization due to the disruptive presence of small additive molecules between adjacent polymer segments would be the predominant phenomenon, and this explains the fall in Tg.

The plot of PVA Tg (from DSC) as a function of lactose content (Fig. 2) indicates a rise in Tg as a result of lactose incorporation. A situation similar to that postulated for the lactose/HPMC system is also believed to exist in the lactose/PVA system. However, an additional factor, thought to be critical, is the rise in the crystallinity of PVA in the presence of lactose (see Fig. 6). Since a rise in film crystallinity is often associated with an elevation in Tg (Droste & Dibenedetto 1969; Okhamafe & York 1985a), it seems, therefore, that the crystallinity factor is mainly responsible for the overall increase in the Tg of PVA in the presence of lactose.

The interpretation given to the ephedrine hydrochloride/HPMC system would also apply to the PVA films containing ephedrine hydrochloride (Fig. 2). In addition, change in crystallinity could be a contributory factor. As shown later in this paper, ephedrine hydrochloride, unlike lactose, lowered PVA crystallinity. This fall in crystallinity may be partly responsible for the decrease in the Tg of PVA as the content of ephedrine hydrochloride was raised.

Softening

The softening point data for both HPMC and PVA film systems are plotted in Fig. 3. In general, softening point decreased as additive concentration was increased. This trend was more pronounced for the polymer/ephedrine hydrochloride system than for the corresponding polymer/lactose system. The depression of softening point in the presence of the additives suggests that the additives exerted a plasticizing effect on the polymer. Although this confirms the preceding findings based on Tg measurements for the polymer/ephedrine hydrochloride films, it is at variance with the conclusions drawn from Tg data in respect of the polymer/lactose films (see Figs 2, 3). The increase in Tg, which indicates a stiffening of PVA by lactose, can be described as an 'anti-plasticizing' action. We are unable at the moment to explain this apparent contradiction but one relevant fact in addition to the difference in measuring techniques is that although glass transition and softening are related, they differ in one fundamental aspect: glass transition is a feature only for the amorphous phase of a polymer while softening is a manifestation of both the amorphous and crystalline phases.

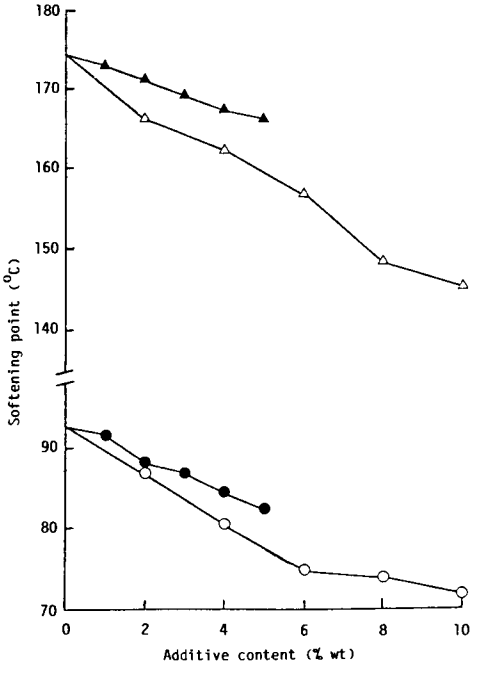

FIG. 3. Softening point of HPMC (△,▲) and PVA (○,●) films containing lactose (closed symbols) and ephedrine hydrochloride (open symbols).

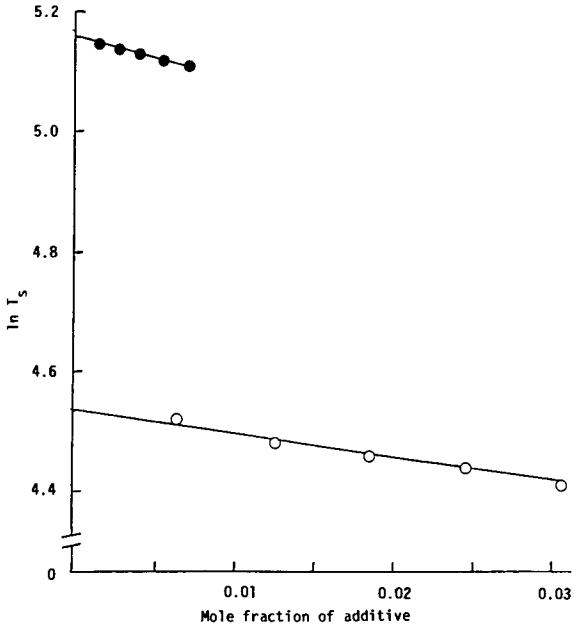

FIG. 4. Plot of the log of softening point of HPMC (●) and PVA (○) films as a function of lactose content.

The softening point data have been further analysed using the empirical relationship (equation 1) of Moelter & Schweizer (1949).

$$T_s = T_o e^{-kn} \quad (1)$$

where T_s and T_o (both in °C) are the softening points of a film with and without an additive, respectively, k the softening point depression coefficient and n the mole fraction of the additive. k, which is obtained from the slope of the linear plot ln Ts versus n is considered a direct measure of plasticizer efficiency. Ln Ts − n plots for the film systems evaluated in the present work are shown in Figs 4, 5. The k values, listed in Table 2, when compared with those of other systems

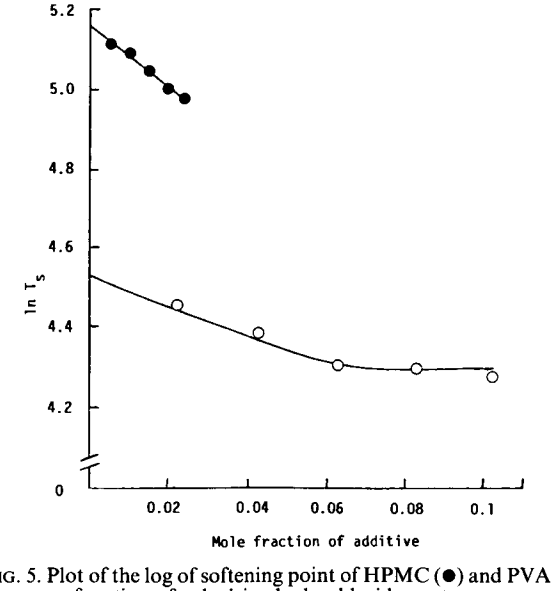

FIG. 5. Plot of the log of softening point of HPMC (●) and PVA (○) films as a function of ephedrine hydrochloride content.

Table 2. Softening point depression coefficients (k) of ephedrine hydrochloride and lactose in HPMC and PVA.

Film	Additive	k	Regression coefficient
HPMC	Ephedrine	7·52	0·994
	Lactose	7·27	0·999
PVA	Ephedrine	3·46	0·999
	Lactose	4·02	0·992

previously reported (Masilungan & Lordi 1984; Okhamafe & York 1988) seem to suggest that lactose and ephedrine hydrochloride are good plasticizers of HPMC and PVA. For example, lactose (k = 7·27) would appear to be a more efficient plasticizer of HPMC than urea with a k value of 5·18 (Okhamafe & York 1988). The untreated softening point data shows that the reverse is the case, with the softening point of HPMC (174·4°C) lowered by urea and lactose to 137·8 and 166·2°C, respectively, at an additive concentration level of 5 wt%. DSC Tg values of 155·8 (HPMC/lactose), 141·5 (HPMC/urea) and 154·6°C (HPMC/lactose) at an additive content of 5 wt% also indicate that urea is the more efficient plasticizer of HPMC. Thus the use of equation (1) in the evaluation of plasticizer efficiency appears to have a major limitation. The relationship was originally proposed for the evaluation of plasticizers in a homologous series (Moelter & Schweizer 1949) and hence the expression of softening point as a function of mole fraction of the plasticizer is appropriate. However, Masilungan & Lordi (1984) have also employed the relationship in a comparative assessment of non-homologous plasticizers. In our view, any comparative evaluation of the plasticizer efficiency of non-homologous additives based on k data that do not take into account the dissimilarity of the molecular or structural units of the additives, is likely to be faced with problems of interpretation. This structural factor is not incorporated in equation (1) which explains why the plasticizer efficiencies derived from the k data for non-homologous additives in an earlier study (Okhamafe & York 1988), as well as the present one, are mostly in conflict with the assessments of plasticizer efficiency based on the corresponding untreated glass transition and softening data.

The compatibility limits of additives in polymers can be determined from ln T_s − n plots (see Figs 4, 5). The additive content at which the curve deviates from linearity is considered the compatibility limit (Moelter & Schweizer 1949). Deviation from linearity occurred only in the plot for the PVA/ephedrine hydrochloride system, giving a compatibility limit of 0·063 (mole fraction) or 6 wt% ephedrine hydrochloride. Compatibility limits for the other systems are apparently higher than the maximum additive concentrations examined in this study.

Melting/decomposition

The melting point of the PVA systems obtained by both DSC and TMA, and the decomposition points of HPMC systems (from TMA only) are recorded in Table 3. Generally, the DSC melting points of PVA were lower than the corresponding values from TMA. This discrepancy, as explained previously (Okhamafe & York 1988), is largely due to the different measuring techniques used. The DSC and TMA

Table 3. Melting points of PVA films and decomposition point of HPMC films containing either ephedrine hydrochloride (EPH) or lactose (LAC).

Content of additive (wt%)	Mp (°C)				Decomp. point (°C)	
	PVA/EPH		PVA/LAC		HPMC/EPH	HPMC/LAC
	DSC	TMA	DSC	TMA		
0	171·7	185·4	171·1	185·4	223·2	223·2
1			171·6	187·3		219·4
2	168·9	182·8	169·3	188·8	221·4	214·4
3			168·4	183·6		212·8
4	166·0	179·9	170·1	179·7	217·2	212·6
5			171·3	173·1		211·1
6	164·2	176·8			209·3	
8	163·3	174·1			207·4	
10	161·3	172·5			206·7	

melting data for the PVA/lactose films also showed conflicting trends when they were plotted as a function of additive content. The TMA data exhibited a small initial rise in the melting point but this was followed by a steady fall as additive level was further raised. On the other hand, the DSC melting point was lowered initially but assumed a slight upward trend with further increase in additive concentration. The reasons for the conflicting trends are not known at the moment. However, both the DSC and TMA melting point results for the PVA/ephedrine hydrochloride system exhibited identical trends, with melting point decreasing as the additive content was raised. It is interesting to note that the effect exerted by ephedrine hydrochloride on PVA melting point is similar to its effect on the Tg and softening point of the same polymer.

The decomposition temperature of HPMC (based on TMA) generally decreased as additive concentration was raised. This tendency was more pronounced for the HPMC/lactose system than for the HPMC/ephedrine hydrochloride system. The intrinsic factors responsible for this phenomenon and its significance in film coating practice are still not clear but it is considered unlikely that the decomposition points were significantly influenced by the fusion of the additives since the melting points of α-lactose monohydrate and ephedrine hydrochloride fall within the range 217–220°C. The decomposition points of the film systems were, in most cases, well below this temperature range.

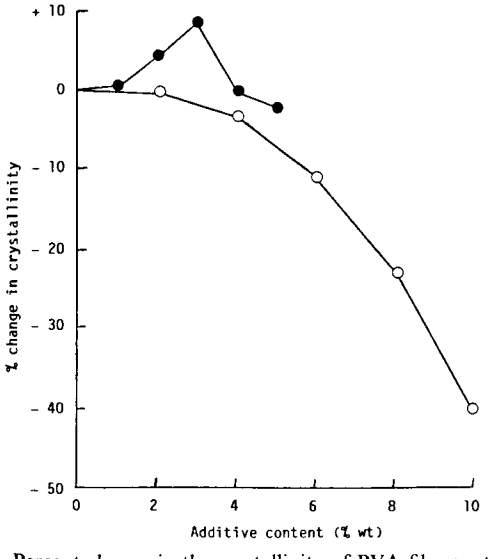

FIG. 6. Percent change in the crystallinity of PVA film containing lactose (●) and ephedrine hydrochloride (○).

Crystallinity

PVA is semi-crystalline (Okhamafe & York 1985a). The area of the fusion endotherm on its DSC thermogram provides a measure of its relative degree of crystallinity. The effect of additive content on PVA crystallinity is illustrated in Fig. 6. The fall of crystallinity with increase in ephedrine hydrochloride content provides a confirmation of the plasticizing activity of the additive in PVA. On the other hand, enhancement of crystallinity by lactose is at least partly responsible for the stiffening (indicated by increase in Tg, see Fig. 2) of PVA in the presence of lactose.

Practical significance

The unintended presence of an excipient of a drug in a film coating (applied to a solid dosage form) as a result of dissolution or migration from the solid dosage core during or after a film coating operation is a distinct possibility. The excipient and drug used in this study are water-soluble and therefore could dissolve in the adsorbed moisture of hydrophilic film coating located in a high humidity environment or in the residual solvent of a film coating prepared from an aqueous formulation. The results obtained indicate the consequences of this phenomenon in film coating practice would be dependent on the nature and extent of interaction between the excipient/drug and film coating polymer. It is generally accepted that plasticization, which manifests as a fall in Tg, Ts and/or crystallinity (Moelter & Schweizer 1949; Okhamafe & York 1985a, b), often lowers the incidence of film coating defects such as cracking, edge splitting and bridging of intagliation (Rowe 1981, 1982). This is usually desirable. However, plasticization could also produce undesirable consequences such as increased film diffusivity to moisture (Okhamafe & York 1983, 1985a) and also to drugs in the case of controlled release products (Rogers 1976). On the other hand, a rise in Tg and crystallinity, as demonstrated by PVA in the presence of lactose, could result in lower film diffusivity (Okhamafe & York 1983, 1985a) and possibly a rise in the incidence of film coating defects due to increased internal stress and film stiffness or rigidity.

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