Interaction Phenomena in some Aqueous-Based Tablet Coating Polymer Systems

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Abstract: Molecular interactions in aqueous-based tabletfilm coating systems consisting of hydroxypropyl methylcellulose (HPMC) in combination with either polyvinyl alcohol (PVA), polyethylene glycol (PEG) 400 or PEG 1000 have been investigated by viscometry and thermal analysis. The viscosity results indicate that the solvent (water) inhibited polymer-polymer interaction and this inhibitory effect was directly related to the solvent affinity of the polymer additive. The presence of crystallinity in the films was examined using a differential scanning calorimeter (DSC). HPMC/PVA blends were partially crystalline but the plasticized HPMC films showed no signs of crystallinity. Glass transition data were also obtained with the DSC. The plasticizer effects of PEG 400 and PEG 1000, respectively, in HPMC were confirmed by the fall in the glass transition temperature (Tg) of HPMC. On the other hand, incorporation of PVA increased the Tg of HPMC, and this was attributed to the presence of a crystalline phase in the blend. Maximum compatibility levels of PVA, PEG 400 and PEG 1000 in the polymer blends were found to be 40, 20 and 15 wt %, respectively, based on glass transition data.

The application of film coatings to solid dosage forms in the pharmaceutical industry has become popular in recent years, and the number of research papers in this area has steadily increased. Most published works, however, have dwelt on end-use properties such as the permeability and mechanical characteristics (1, 2). Insufficient attention appears to have been given to the intrinsic properties of the film coating systems. Since film coating components are often polymeric in origin, their structures and interactions are often complex. A satisfactory study of film properties would be incomplete if it did not include examination of interactions at the molecular level. Some of the techniques available for characterizing molecular interactions include infra-red spectroscopy, nuclear magnetic resonance, X-ray diffraction and photon correlation spectroscopy. The techniques employed in the present study are viscometry and thermal analysis.

Viscosity studies offer a convenient and simple way of investigating interaction and compatibility phenomena in binary polymer systems (3, 4). Although quantifying these phenomena often proves a difficult task, viscometry nonetheless provides an insight into inter-molecular activities. Crystallinity and glass transition temperature are two of the parameters that can be obtained from thermal analysis (5, 6). The significance of crystallinity lies in the rigid and impermeable nature of the crystalline region of a polymer. Michaels and Bixler (7) have observed that an increased degree of film crystallinity leads to reduced diffusivity in polyethylene. The glass transition temperature is generally regarded as the characteristic temperature at which a polymer changes from a state of relative molecular or segmental rigidity (glassy phase) to one of considerable chain mobility (rubbery phase). The transition is observable in differential scanning calorimetry as an endothermal shift in the baseline of a thermogram. Burrell (8) reported that a change in glass transition temperature usually affected such film properties as permeability, tensile strength and elastic modulus. Plasticization lowered glass transition temperature and mechanical properties. However, diffusivity may be reduced or enhanced depending on the plasticizer type and content. On the other hand, induction of steric hindrance, closer packing or restriction of segmental motion will be likely to result in an increase in glass transition temperature (9).

Polymer systems consisting of hydroxypropyl methylcellulose in combination with either polyvinyl alcohol (PVA), polyethylene glycol (PEG) 400 or PEG 1000 are examined in this paper.

Materials and Methods

Pharmacoat 606 (hydroxypropyl methylcellulose or HPMC) and Poval PA-5 (polyvinyl alcohol or PVA with a degree of hydrolysis of 88 %) were manufactured by Shin-Etsu Chemical Co. Ltd., Japan. The plasticizers, polyethylene glycol (PEG) 400 and PEG 1000, were supplied by British Drug Houses, Poole, U.K.

Viscosity

The concentration of polymer solutions ranged from 0.05–0.5 % w/v in double-distilled water. Three binary polymer systems were evaluated. Each contained HPMC and in addition, either PVA, PEG 400 or PEG 1000 in concentration of up to 80 wt % based on HPMC content. The mixed polymer solutions were filtered through a sintered glass filter grade 3 and their viscosities measured with a Cannon-Ubbelohde size 50 viscometer at 25°C. The method employed satisfies the requirements of BS 188: 1977[3] and ASTM D2857-70[4]. Kinetic energy corrections were not made because flow times exceeded 200 seconds in all cases. Plots of inherent viscosity (logarithmic viscosity number) against concentration were extrapolated to zero concentration in order to obtain intrinsic viscosity.

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[3] BS 188: British Standard Methods for determination of the viscosity of liquids (1977), British Standards Institution.
[4] Annual Book of ASTM Standards (1983), Vol. 08.02, pp. 640–646, American Society for Testing Materials, Philadelphia.

Crystallinity

Films were cast on the inside of a lipped Perspex cylinder and conditioned as described in a previous study (10) from 10% w/v aqueous mixtures containing HPMC and varying amounts of either PVA, PEG 400 and PEG 1000. Film discs were punched from the films and a sample weighing approximately 20 mg contained in a crimped aluminium sample pan with pierced lid, was program-heated in a nitrogen environment at 10°C/min in a DuPont 1090 differential scanning calorimeter (DSC) to 125°C and held at this temperature for five minutes in order to remove any moisture whose endotherm could possibly overlap with the desired thermal transitions. After quench cooling with liquid nitrogen to room temperature, the sample was reheated to 300°C at 10°C/min. The heat of transition of any melting endotherms observed on the thermograms were calculated with the aid of the DuPont V2.0 data analysis program. Duplicate measurements were made.

Glass Transition

Film samples were prepared for DSC as above. Each sample was heated to, and kept at, 125°C for ten minutes under a nitrogen gas purge, to minimize the possibility of any glass transitions being masked by thermal events arising from moisture evolution from the sample. It was quenched cooled to, and left at, −40°C for five minutes and then reheated at 20°C/min to 250°C. Glass transitions were determined from the thermograms of reheated samples. Thermograms were also obtained for PEG 400 and PEG 1000 in their original liquid and solid forms, respectively, (since they could not on their own form coherent films) as well as the plasticized HPMC film between −120 and 80°C. For HPMC films containing PVA and 5 wt% of plasticizer, the DuPont 1090 V2.0 analysis program was used to analyze glass transition. At plasticizer concentrations above 5 wt%, the glass transitions were usually broad and complex, and in such cases analysis was carried out manually as illustrated in Fig. 1. The heat capacity change at glass transition (ΔC_H) is the change in heat capacity between the onset and the end of glass transition while the intersection of the mid-point of ΔC_H with a straight line joining the onset and end of glass transition was taken as the glass transition temperature (T_g) of the film. All measurements were in quadruplicate, and the mean was taken.

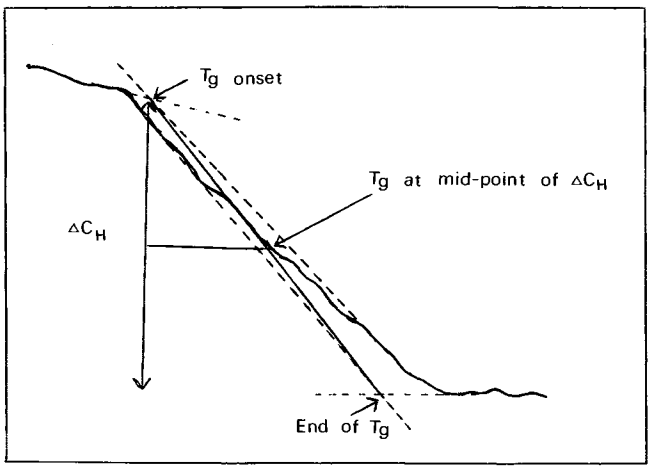

Fig. 1 Manual calibration of glass transition thermogram.

Results and Discussion

Viscosity

The intrinsic viscosity of a binary polymer system is usually considered as the intrinsic viscosity of a polymer, X, in a 'solvent system' which is actually a dilute solution of another polymer, Y, in a pure solvent (11). Where this value differs from the intrinsic viscosity of polymer X in the pure solvent, the difference can be attributed to interactions involving the two polymers and the solvent as a result of which the molecular dimensions of polymer X are altered. Thus the intrinsic viscosity, $[\eta_X]_{C_Y}$, of the polymer blend may be expressed as follows (11):

$$[\eta_X]_{C_Y} = \lim_{C_X \to 0} \frac{\eta(C_X, C_Y) - \eta(CC_Y)}{\eta_{(C^Y)} \quad C_X} \qquad (1)$$

where $\eta_{(C_x,C_Y)}$ is the viscosity of the polymer blend, $\eta_{(C_Y)}$ is the viscosity of polymer Y in the pure solvent, and C_X and C_Y are the concentrations of X and Y, respectively. If the ratio $\frac{[\eta_X]}{[\eta_X]_{C_Y}}$ is less than unity (where $[\eta_X]$ is the intrinsic viscosity of polymer X in the pure solvent), then the chain dimension of polymer X has been reduced as a result of the presence of polymer Y. The reverse applies if the ratio is greater than unity.

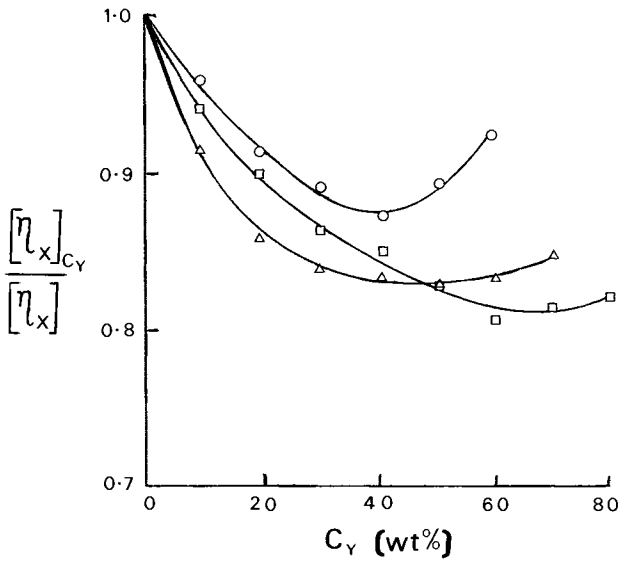

Fig. 2 Variation of the intrinsic viscosity of HPMC in a solution containing either PVA (○), PEG 400 (□) or PEG 1000 (△) at 25°C.

Fig. 2 shows a plot $\frac{[\eta_X]}{[\eta_X]_{C_Y}}$ versus concentration (C_Y) of polymer Y (PVA, PEG 400 or PEG 1000) as weight percent of HPMC (polymer X). The molecular chains of HPMC in a dilute solution (in the pure solvent) are fully uncoiled and hence have attained maximum dimensions. In this state, hydrogen bonds are formed with the solvent (water) but intra- and intermolecular interactions are minimal. As Fig. 2 shows, the effect of any one of the added polymers is initially to decrease the intrinsic viscosity (and hence the molecular dimensions) of HPMC. This is attributed to interaction by hydrogen bonding between the added polymer and the solvent which occurs largely at the expense of hydrogen bonding between HPMC and the solvent. Thus the molecular segments

of HPMC retract and this further enhances intra- and intermolecular interactions of this polymer. Intrinsic viscosity minima were observed at the following contents of the polymer additives: 40 wt % (PVA), 50 wt % (PEG 1000) and 60 wt % (PEG 400). It appears that when these respective levels were exceeded, there was greater interaction between the polymer additives and the HPMC, and this increased the molecular dimensions of the latter and hence its intrinsic viscosity.

A correlation exists between the position of the intrinsic viscosity minima and the structure of the polymer additives. The rank order of appearance of the minima with increase in additive concentration is: PVA → PEG 1000 → PEG 400. The PEG's (being glycols) have twice the number of hydroxyl groups of PVA and therefore have more affinity for the solvent than the latter. Hence greater amounts of the PEG's than PVA would need to be added in order to reach the levels at which the polymer additive begins to interact with HPMC. For similar reasons, the more hydrophilic (shorter hydrocarbon backbone) PEG 400 has its intrinsic viscosity minimum at a higher concentration level than PEG 1000. An identical correlation was also observed between the magnitude of the intrinsic viscosity minima (i.e. the maximum depression of the intrinsic viscosity of HPMC) and the structure of the additives. The greater the affinity of the polymer additive for (and thus its interaction with) the solvent the greater the maximum reduction in the molecular dimensions of HPMC and consequently, the lower is the intrinsic viscosity minimum.

It is apparent from this discussion that when blending polymers, the solvent employed is of great importance. The most appropriate solvent would be one whose interaction with either of the polymers in the blend does not exceed that between the two polymers. Polymer-polymer interaction could also be improved by introducing favorable functional groups into one or both of the polymers.

Crystallinity

Ideally, for the samples to have a well defined thermal history, the rates of cooling and re-heating should be the same. This applies to the crystallinity as well as the glass transition determinations. Quench cooling was, however, carried out because the DSC employed did not have a controlled cooling facility. In addition, although it is common in glass transition measurements to pre-heat samples above the glass transition temperature, this technique was not used in the present study because in many cases when it was employed, the thermograms obtained did not show glass transitions. Nonetheless, both the crystallinity and glass transition data shown in this paper are judged to be reliable guides to polymeric interactions in the films examined.

The thermogram for HPMC film showed an endothermic peak between 220 and 260°C but this transition disappeared when HPMC was bended with either PVA, PEG 400 or PEG 1000. However, another melting transition (corresponding to that due to PVA) was observed in HPMC/PVA thermograms between 140 and 200°C. Since only the crystalline region of a polymer undergoes a melting transition (12), it may be inferred that HPMC films plasticized with the PEG's were virtually 100 % amorphous (non-crystalline). The heat of transition, calculated from the area of the melting endotherm, thus provides a good estimate of the degree of crystallinity within a series of identical polymers or polymer blends.

Table I shows the heats of transition and the crystallinity data for HPMC/PVA blends. Since 100 % crystalline PVA could not be obtained, the comparative crystallinity indices are based on PVA film as standard. The results indicate that between 10 and 30 wt % PVA, the crystallinity of the film blends was practically unchanged, but increased with further rise in PVA content. The relatively large increase in crystallinity between 40 and 60 wt % PVA was probably due to the presence of free PVA when the compatibility level of PVA with HPMC was exceeded.

Table I. Comparative crystallinity data for HPMC/PVA film systems

Polymer additive (wt %)	Heat of transition (Jg^{-1}) ± m.d.[a]	Comparative crystallinity index (%)
PVA 10	5.86 ± 0.54	17.5
PVA 20	6.31 ± 0.70	18.8
PVA 30	5.99 ± 0.53	17.8
PVA 40	7.26 ± 0.37	21.6
PVA 50	9.45 ± 0.65	28.1
PVA 60	13.12 ± 1.16	39.0
PVA alone	33.60 ± 0.60	100.0
HPMC alone	32.31 ± 0.66	

[a] mean deviation

Partially-crystalline films are analogous to filled films (13) with the crystallites, being impermeable to diffusants, behaving like filler particles and therefore increasing the tortuosity of the diffusion pathways. Thus the crystallinity data confirm the suggestion made in an earlier study (10) that the decrease in the diffusion coefficient in these systems might be due to the effect crystallinity.

Glass Transition Temperature

Couchman (14) derived a relationship (equation (2)) for predicting the glass transition temperature (T_{g_B}) of a compatible polymer blend.

$$T_{g_B} = \frac{M_X \Delta C_{H_X} \ln T_{g_X} + M_Y \Delta C_{H_Y} \ln T_{g_Y}}{M_X \Delta C_{H_X} + M_Y \Delta C_{H_Y}} \quad (2)$$

where X and Y, respectively, are the two components of the blend; M_X and M_Y are their respective mass fractions; and T_{g_X}, T_{g_Y}, ΔC_{H_X} and ΔC_{H_Y} are the glass transition temperatures and heat capacity change at glass transitions, respectively, of the pure components. The Couchman equation is thermodynamically-based and is applicable to wholly or largely amorphous polymers. Although equation (2) does not take into account the water content of the films, it was nevertheless considered adequate for predictive purposes.

Experimental and predicted (Couchman) values of glass transition temperature (T_g) as well as the glass transition spread (T_g spread) for the three polymer blends examined are plotted in Figs. 3–5. Table II shows the glass transition temperatures (T_g) and the heat capacity change at glass transition (ΔC_H) of the individual polymers, and also he glass transition temperature of the polymer additives in the blends when the compatibility limit was exceeded. The T_g of PEG 1000 was estimated on the basis of an empirical relationship proposed by Beaman (12) because glass transition could not be detected in its thermogram. The ΔC_H value for PEG 1000 was assumed to be the same as that for PEG 400 since Couchman (14) observed that this parameter was generally similar for structurally related polymers. Film blends of HPMC/PEG 400

Table II. Glass transition temperature (T_g) and heat capacity change at glass transition (ΔC_H) of the individual polymers, and T_g of polymeric additives in the film systems above the compatibility limits

Polymer content (wt %)		T_g (°C)	ΔC_H ($Jg^{-1} K^{-1}$)
HPMC alone		155	0.1401
PEG 400 alone		− 66	0.3007
PEG 1000 alone		28[a]	0.3007[a]
PVA alone		73	0.3740
PEG 400	25 %	− 48	
PEG 400	30 %	− 50	
PEG 1000	20 %	melting	
PEG 1000	25 %	endotherms	
PEG 1000	30 %	observed	
PVA	60 %	73	

[a] estimated

and HPMC/PEG 1000 (Figs. 3 and 4) generally followed the trend predicted by the Couchman relationship. This observation is consistent with the well known plasticizing activity of the PEG's when blended with HPMC. The increased segmental mobility of HPMC caused by plasticization would normally be expected to result in the depression of the temperature at which transition from a glassy to a rubbery state occurs. This is supported by the results obtained. On the other hand, the experimental T_g data for HPMC/PVA blends (Fig. 5) are contrary to those predicted by equation (2). Though hydrogen bonding is likely to be involved in the interaction between the polymeric components of the blend, plasticization is not evident. The most probable explanation is that the crystalline phase of PVA, in the form of rigid solid entities (crystallites), restricted the molecular mobility of the blend hydrodynamically and by interacting with the compatible phase of the film. Thus a direct relationship exists between the crystallinity data in Table I and the experimental Tg data for HPMC/PVA blends. This is in agreement with the reported increase in the T_g of many polymers with increase in film crystallinity (15).

Figs. 2–4 and Table II also provide useful information on the compatible characteristics of the polymer blends. As the content of polymer additive increased, the T_g spread (i.e. the temperature range over which glass transition occurs) also

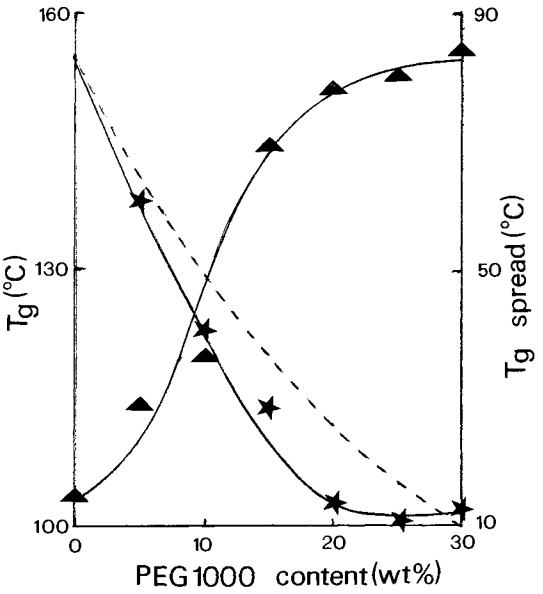

Fig. 4 Glass transition plots for HPMC/PEG 1000 films.
★ = Experimental glass transition temperature (T_g)
--- = Predicted glass transition temperature (T_g)
▲ = Glass transition spread (T_g spread)

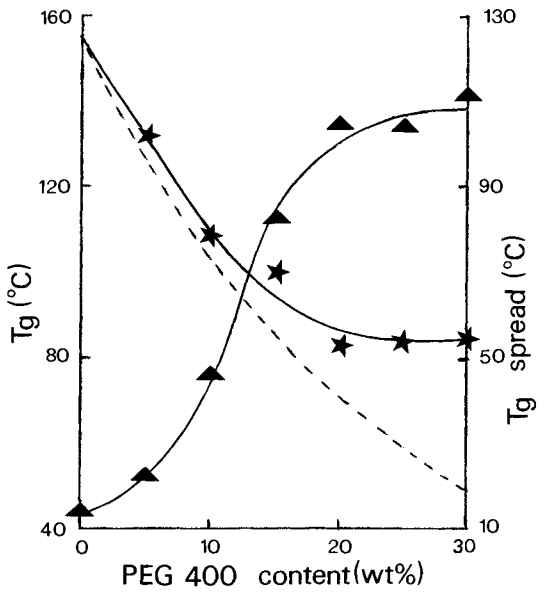

Fig. 3 Glass transition plots for HPMC/PEG 400 films.
★ = Experimental glass transition temperature (T_g)
--- = Predicted glass transition temperature (T_g)
▲ = Glass transition spread (T_g spread)

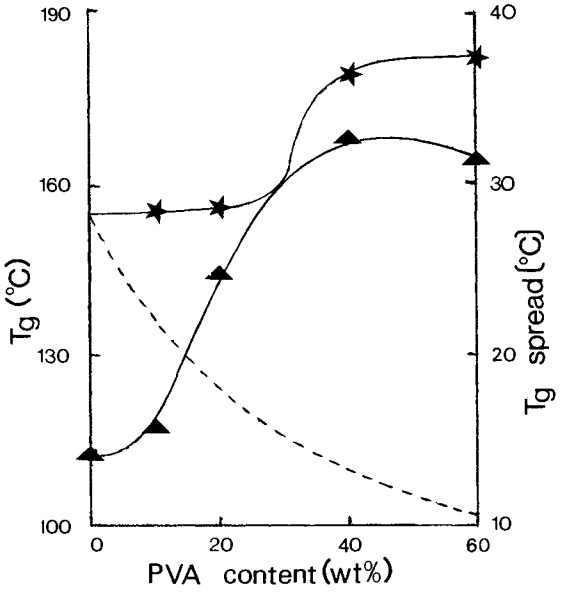

Fig. 5 Glass transition plots for HPMC/PVA films.
★ = Experimental glass transition temperature (T_g)
--- = Predicted glass transition temperature (T_g)
▲ = Glass transition spread (T_g spread)

increased. This is a characteristic feature of polymers which are not compatible in all proportions (9), and it eventually leads to the appearance of two glass transitions when the compatibility limit is exceeded: one for the compatible phase and the other for the excess polymer additive. (Because the glass transition of PEG 1000 could not be detected, the appearance of its melting endotherm was considered as indicating incompatibility). T_g spread changed very little above the compatibility level. Incompatibility results when the solubility limit of the polymer additive in the main polymer is exceeded. Above this limit, two phases are formed: main polymer/polymer additive and polymer additive alone. Based on the concentration of the polymer additive at which a second glass transition (melting endotherm in the case of PEG 1000) was first observed, the polymer mixtures are compatible up to the following concentration of the additives: 40 wt % (PVA), 20 wt % (PEG 400) and 15 wt % (PEG 1000).

The difference between the experimental and predicted T_g data for the plasticized systems may be due, in part, to large variations in the molecular weight distributions of the polymers as has been noted by Entwistle and Rowe (16). Molecular weight variations may also explain the complex thermograms observed at plasticizer concentrations above 5 wt %.

Abbreviations and Symbols

HPMC	= Hydroxypropyl methylcellulose
PVA	= Polyvinyl alcohol
PEG	= Polyethylene glycol
X	= Main film former, i.e. HPMC
Y	= Polymer additive
C_X	= Concentration of HPMC
C_Y	= Concentration of polymer additive
$\eta(C_X, C_Y)$	= Viscosity of polymer blend
$[\eta_X]_{C_Y}$	= Intrinsic viscosity of polymer blend
$[\eta_X]$	= Intrinsic viscosity of polymer X in pure solvent
$\eta_{(C_Y)}$	= Viscosity of polymer Y in pure solvent
B	= Polymer blend
M	= Mass fraction
T_g	= Glass transition temperature
ΔC_H	= Heat capacity change at glass transition

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In Vitro and *In Vivo*-Release of Nitroglycerin From a New Transdermal Therapeutic System

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Abstract: A new transdermal therapeutic system (TTS) for nitroglycerin is presented that controls release of the active substance by means of desorption and diffusion. The drug release, in the dosage range examined under sink conditions, is independent of electrolytes and pH of the aqueous acceptor medium, but it does depend on its temperature as expected. Batches obtained on a production scale were highly reproducible. The validity of an *"in vitro"* dissolution model is demonstrated by the good correlation between the amount of nitroglycerin liberated *"in vitro"* and *"in vivo"*. The amount of nitroglycerin released *in vivo* is approximately 10 µg/cm²/h from 4 hours after application, and, it is controlled by the system. The plasma concentration reaches a maximum of 255 ± 151 pg/ml at 2 hours after drug application followed by a plateau level of 125 ± 50 pg/ml which is maintained between 8 and 24 hours after application. In a crossover study with a reference product characterized by the same release rate *in vivo* of 5 mg/24 h, both transdermal therapeutic systems proved to be bioequivalent.

Transdermal Therapeutic Systems (TTS) combine the principle of percutaneous application of drugs in order to avoid the first-pass effect after oral administration with the attainment of active drug levels sustained for 24 h or more (1). In order to control the absorption of the active substance, the release of active substance from the TTS should be the rate limiting step of the *in vivo* release. If the transdermal absorption rate is too

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