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β-Cyclodextrins influence on *E*-3,5,4′-trimethoxystilbene absorption across biological membrane model: A differential scanning calorimetry evidence

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ABSTRACT

E-3,5,4′-trimethoxystilbene (TMS) is a naturally occurring analog of resveratrol. The anti-neoplastic, antiallergic and anti-angiogenic activities of TMS have been recently reported. From the viewpoint of metabolism, TMS may be more favourable than resveratrol because all of its hydroxyl groups, which are subjected to extensive glucuronide or sulphate conjugation in the metabolic pathways of resveratrol, are protected by methylation. Moreover, methylation increases lipophilicity and may enhance cell membrane permeability, but it decreases its solubility in aqueous media. A way to increase TMS solubility can be represented by complexation with β-cyclodextrins. In the present paper, the differential scanning calorimetry technique has been used to study the interaction of TMS with a biomembrane model constituted by dimyristoylphosphatidylcholine multilamellar vesicles. Furthermore, kinetic experiments have been carried out to follow the uptake of TMS by biomembranes in the presence of β-cyclodextrins to gain information on the effect of β-cyclodextrins on the uptake process. Our results indicate that opportune concentrations of β-cyclodextrins greatly improve the uptake of TMS by biomembrane models.

1. Introduction

E-3,5,4′-trimethoxystilbene (TMS) is a naturally occurring analog of resveratrol (Scheme 1) (Blair et al., 1969; MacRae and Towers, 1985). The anti-neoplastic, antiallergic and anti-angiogenic activities of TMS have been recently reported (Bader et al., 2008; Belleri et al., 2005; Pan et al., 2008). From the viewpoint of metabolism, TMS may be more favourable than resveratrol because all of its hydroxyl groups, which are subjected to extensive glucuronide or sulphate conjugation in the metabolic pathways of resveratrol (Lançon et al., 2007), are protected by methylation. Moreover, methylation increases lipophilicity and may enhance cell membrane permeability. Hence, improved pharmacokinetic profile, could be postulated. On the other hand, methylation decreases aqueous solubility and could hinder the oral bioavailability of TMS. In a previous paper (Sarpietro et al., 2007) we compared the interaction and the absorption of resveratrol and two analogs (TMS and 3,5,4′-tri-*O*-triacetylresveratrol) with biomembrane model. From this study it emerged a strong interaction of TMS with the biomembrane model but a very poor absorption. Therefore, it should be of interest to use cyclodextrins to increase the aqueous solubility of TMS and hence its absorption by biomembrane model.

Cyclodextrins (CD) are a family of cyclic oligosaccharides, obtained from starch by enzymatic degradation, composed of α-1,4-linked glucopyranose subunits (Uekama, 2004). These macrocyclic carbohydrates possess apolar internal cavities which can form complexes with various guest molecules via non-covalent interactions; the binding of guest molecules with the CD host is not permanent but rather it is a dynamic process whereby the guest molecule continuously associates and dissociates from the CD host (Lesieur et al., 2000; Shimpi et al., 2005). Because of their properties, CD are widely used in several fields. In particular, hydrophilic CD can lead to enhanced solubility, dissolution rate, membrane permeability and bioavailability of poorly water-soluble drugs (Másson et al., 1998; Redenti et al., 2001; Karathanos et al., 2007). Furthermore, CD possess most of the characteristics (quality, cost performance, bioadaptability, and negligible toxic effects) required for drug carriers from the safety viewpoint (Szejtli, 1998).

β-CD, which are composed of seven α-1,4-linked glycosyl units, are the ones most commonly used for pharmaceutical applications since their central cavity has good affinity for many hydrophobic drug compounds (Loftsson et al., 2005; Singh et al., 2002). In this research, we have performed different series of experiments to detect the interaction between TMS and dimyristoylphosphatidylcholine (DMPC) multilamellar vesicles (MLV) used as biomembrane models and to follow the uptake of TMS by the biomembrane models with and without β-CD, with the aim to demonstrate that the presence of β-CD improves the uptake process.

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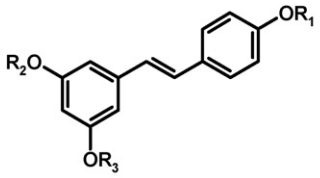

	R_1	R_2	R_3
Resveratrol	H	H	H
***E*-3,5,4'-trimethoxystilbene**	CH_3	CH_3	CH_3

Scheme 1. Resveratrol and *E*-3,5,4′-trimethoxystilbene structure.

DMPC MLV are characterized by a sharp phase transition from an ordered gel-like structure to a disordered fluid-like structure upon heating. This phase change happens at a characteristic transition temperature (T_m), revealed by the differential scanning calorimetry (DSC) technique as an endothermic peak associated to the enthalpy change (ΔH). The presence of foreign substances dissolved in the phospholipid bilayers modifies the MLV thermotropic parameters (T_m, ΔH) the effects being related to the amount of compound dissolved in the phospholipid matrix (Mabrey-Gaud, 1981; Silvius, 1991; Bach, 1984; Marsh, 1996; Huang and Li, 1999). The interaction and the absorption of TMS by the MLV have been monitored via the modification of the T_m and ΔH due to the molecule insertion in the MLV phospholipid bilayers.

2. Materials and methods

2.1. Materials

Reagents were of commercial quality and were used as received (Merck and Sigma–Aldrich); only solvents were distilled using standard techniques. The ^{1}H NMR spectra were recorded on a Varian Unity Inova spectrometer at 500 MHz and performed at constant temperature (27 °C). Analytical thin-layer chromatography was performed on silica gel (Merck 60 F254) plates using cerium sulphate as developing reagents.

β-CD (purity ≥99%) were purchased from Fluka (Germany). 1,2-Dimyristoyl-sn-glycero-3-phosphatidylcholine (purity = 99%) was supplied by Genzyme Pharmaceuticals (Liestal, Switzerland). Lipids were chromatographically pure as assessed by two-dimensional thin-layer chromatography. 50 mM tris(hydroxymethyl)aminomethane (TRIS) solution, adjusted to pH 7.4, was employed.

TMS was synthesized, as previously reported, through on a Arbuzov rearrangement followed by Horner–Emmons–Wadsworth reaction; spectral data are in perfect agreement with those obtained previously (Spatafora et al., 2009).

2.2. DSC analysis

A Mettler Toledo STAR^e system equipped with a DSC-822^e calorimetric cell and a Mettler TA-STAR^e software was used. The sensitivity was automatically chosen as the maximum possible by the calorimetric system, and the reference pan was filled with TRIS solution. The calorimetric system was calibrated, in transition temperature and enthalpy changes, by using indium, stearic acid, and cyclohexane by following the procedure of the DSC 822 Mettler TA STAR^e instrument.

2.3. Liposome preparation

Stock solutions of DMPC and *E*-3,5,4′-trimethoxystilbene in chloroform/methanol (1:1, v/v) were prepared. Aliquots of DMPC solution were distributed in glass tubes to have the same amount of DMPC in all of the tubes; then aliquots of TMS solution were added to have a defined molar fraction (X) (0.00, 0.015, 0.03, 0.045, 0.06, 0.09, 0.12 and 0.15) of the examined compound with respect to the phospholipid. The solvents were removed under nitrogen flow, and the resulting films were dried under vacuum to eliminate eventual solvents residues. TRIS solution was added to the films (to have 0.06125 mmoles/ml of phospholipid), and the samples were heated at 37 °C for 1 min and successively shaken for 1 min, for three times, and kept at 37 °C for 1 h to permit the MLV to homogenize and allow the compounds to partition between phospholipid and aqueous phases.

2.4. TMS/MLV interaction

120 μl of MLV with or without TMS was transferred into a 160 μl aluminum DSC pan, which was sealed, and submitted to calorimetric analysis as follows: (i) a heating scan between 5 and 37 °C at 2 °C/min; (ii) a cooling scan between 37 and 5 °C at 4 °C/min; for at least four times to check the results reproducibility. After the DSC analysis, aliquots of all samples were extracted from the calorimetric aluminum pans and used to determine, by the phosphorus assay (Rouser et al., 1970), the exact amount of phospholipids present in each sample.

2.5. Kinetic experiments

These experiments were carried out according to four experimental patterns: (i) in order to evaluate the TMS ability to diffuse through the aqueous medium, reach the biomembrane model and cross it, an exact amount of powdered TMS (to have a 0.12 molar fraction of compound with respect to the phospholipid) was weighed in the bottom of the DSC pan where 120 μl of DMPC MLV aqueous dispersion was added; (ii) in order to evaluate the possibility to increase the rate and extent of these processes, the previously described kinetic measurements were also done in the presence of β-CD solutions, keeping unchanged the TMS molar fraction (0.12) and varying the amount of β-CD in order to get 1:0.5, 1:1, 1:2, TMS/β-CD molar ratios; (iii) to monitor eventual interactions between MLV and β-CD, powdered β-CD (to have the same amount used in the above experiments) was weighted in the bottom of the DSC pan and added with 120 μl of DMPC MLV aqueous suspension; (iv) to detect the stability of the TMS dispersion in the lipid matrix and the β-CD capability to extract the compound from DMPC MLV, kinetic experiments were also carried out on DMPC MLV loaded with 0.12 molar fraction of TMS left in contact with solid β-CD to have 1:0.5, 1:1, 1:2 TMS/β-CD molar ratios. The samples were hermetically sealed and gently vortexed for a couple of seconds, and the interaction between TMS and DMPC (with or without β-CD) and between β-CD and DMPC was detected submitting the samples to the following calorimetric analysis: (a) a heating scan between 5 and 37 °C at the rate of 2 °C/min; (b) an isothermal period (1 h) at 37 °C; and (c) a cooling scan between 37 and 5 °C at the rate of 2 °C/min.

The procedure was repeated eight times to follow the variations in the calorimetric curves, which indicate an interaction between the tested compounds and the DMPC bilayers occurs.

3. Results and discussion

It has been reported that TMS, due to its lipophilicity, is unable to migrate towards the aqueous medium and interact with biomem-

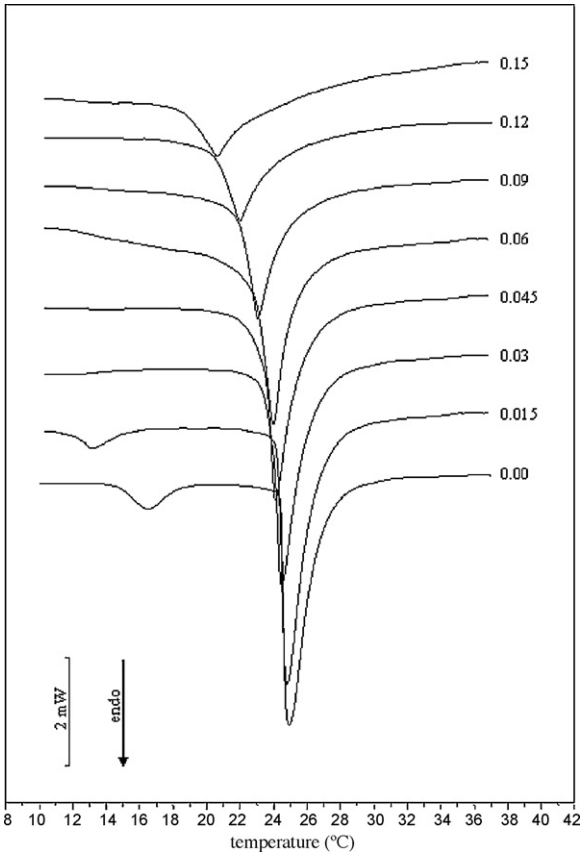

Fig. 1. Calorimetric curves, in heating mode, of DMPC MLV prepared in the presence of increasing molar fractions of TMS.

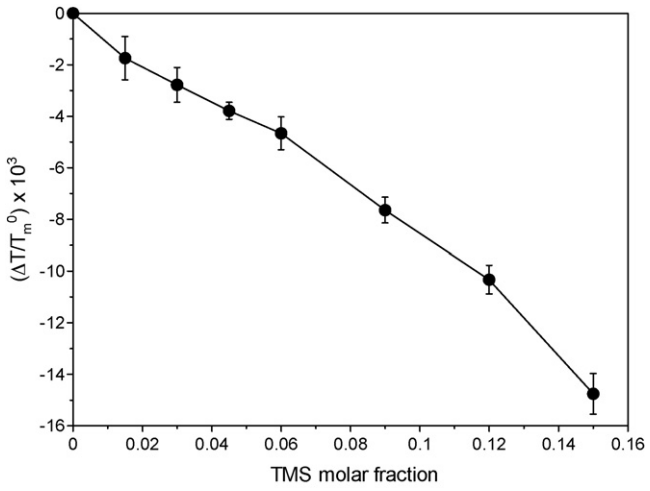

Fig. 2. Transition temperature, as $\Delta T/T_m^0$, of DMPC MLV prepared in the presence of increasing molar fractions of TMS, as a function of TMS molar fraction in the MLV aqueous dispersion. $\Delta T = T_m - T_m^0$, where T_m^0 is the transition temperature of pure DMPC MLV and T_m is the transition temperature of DMPC MLV prepared in the presence of TMS.

brane model (Sarpietro et al., 2007). Pharmacokinetic studies of TMS formulated with hydroxypropil–β-cyclodextrins have also been carried out (Lin and Ho, 2009) but nothing has been reported on TMS ability to interact with biomembranes in the presence of β-CD. In this paper, we investigated, by means of DSC, the capability of TMS to interact with a biomembrane model constituted by DMPC MLV and the transfer kinetics of TMS from the aqueous medium into the phospholipid bilayers, in the presence of different amounts of β-CD, in order to demonstrate that β-CD favour the transfer process. The procedure previously described to study the interaction of bioactive compounds with DMPC MLV (Castelli et al., 1999a,b, 2000; Sarpietro et al., 2005) has been followed. The calorimetric analyses have been taken in the temperature range between 5 and 37 °C, where DMPC exhibits a small calorimetric peak (the pretransition peak) at about 16.5 °C, related to the hydrophobic chains tilt and a main calorimetric peak at 24.8 °C, associated with the phase transition from an ordered gel state to a disordered liquid–crystalline state (Walde, 2004; Gardikis et al., 2006). The calorimetric curves of DMPC MLV alone, or prepared in the presence of increasing molar fraction of TMS, are reported in Fig. 1. TMS interaction with the biomembrane model is demonstrated through the variation of the MLV thermotropic behaviour. TMS causes the pretransition peak to disappear while the main transition peak gradually broadens and shifts toward lower temperature. The T_m values obtained from the calorimetric curves have been plotted in Fig. 2 as $\Delta T/T_m^0$ ($\Delta T = T_m - T_m^0$, where T_m is the transition temperature of DMPC vesicles in presence of TMS, while T_m^0 is the transition temperature of pure DMPC MLV) against the TMS molar fraction in the MLV aqueous dispersion. It is evident that TMS decreases the T_m proportional to its concentration within the MLV. The disappearance of the pretransition peak, the broadening and the shift of the main peak are clear signs of the interaction between TMS and MLV bilayers in a concentration-dependent way. These results are considered as the maximum effect caused by the TMS on MLV are employed as reference in the following experiments to monitor the TMS transfer from the solution to the biomembrane model.

Permeation kinetic experiments have been carried out leaving DMPC MLV in contact with TMS to evaluate the capability of the TMS to pass through the aqueous medium, reach the MLV surface, and enter into the MLV. TMS is a hydrophobic compound, then, kinetic experiments with MLV and TMS in the presence of increasing amounts of β-CD, as a solubilising agent, have been carried out to determine if β-CD favour the TMS dissolution and the migration rate, by the formation of inclusion complexes (Del Valle, 2004). This procedure should allow the TMS to easily reach the MLV outer layer, and, hence, to be absorbed. As said above, the interaction between a chemical compound and the MLV is revealed by a change in the thermodynamic parameters of the calorimetric curves with respect to that of pure DMPC MLV. Then, to ascertain that, in the experiments carried out with TMS and β-CD, the effect exerted on MLV thermotropic behaviour is ascribed to TMS alone, control experiments have been performed in the presence of β-CD alone at the same concentration used in the kinetic experiments involving both TMS and β-CD. The curves (not shown) of these control experiments do not show variation with respect to the pure DMPC demonstrating that the low amounts of β-CD chosen by us and usually employed to form inclusion complexes (1:1 molar ratio) (Szejtli et al., 1980; Loftsson et al., 2005) can be added without modifying the DMPC phase transition. Thus, we are excluding any effect of β-CD on DMPC when they are employed together with TMS, allowing us to attribute the observed effects on the DMPC phase transition to TMS alone.

The calorimetric curves of the kinetic experiments with TMS (0.12 molar fraction), without and with different amount of β-CD, are shown in Fig. 3A–D and compared with the calorimetric curve of DMPC MLV and the calorimetric curve of DMPC MLV prepared in the presence of TMS at 0.12 molar fraction (this is the curve that should be obtained if the TMS was completely absorbed by MLV). A 0.12 molar fraction was used as, in the TMS/MLV interaction experiments, it caused a high transition temperature associated with a well defined calorimetric peak of DMPC MLV without phase separation, which was instead present in the calorimetric curve related to 0.15 molar fraction. TMS (Fig. 3A) alone does not cause important

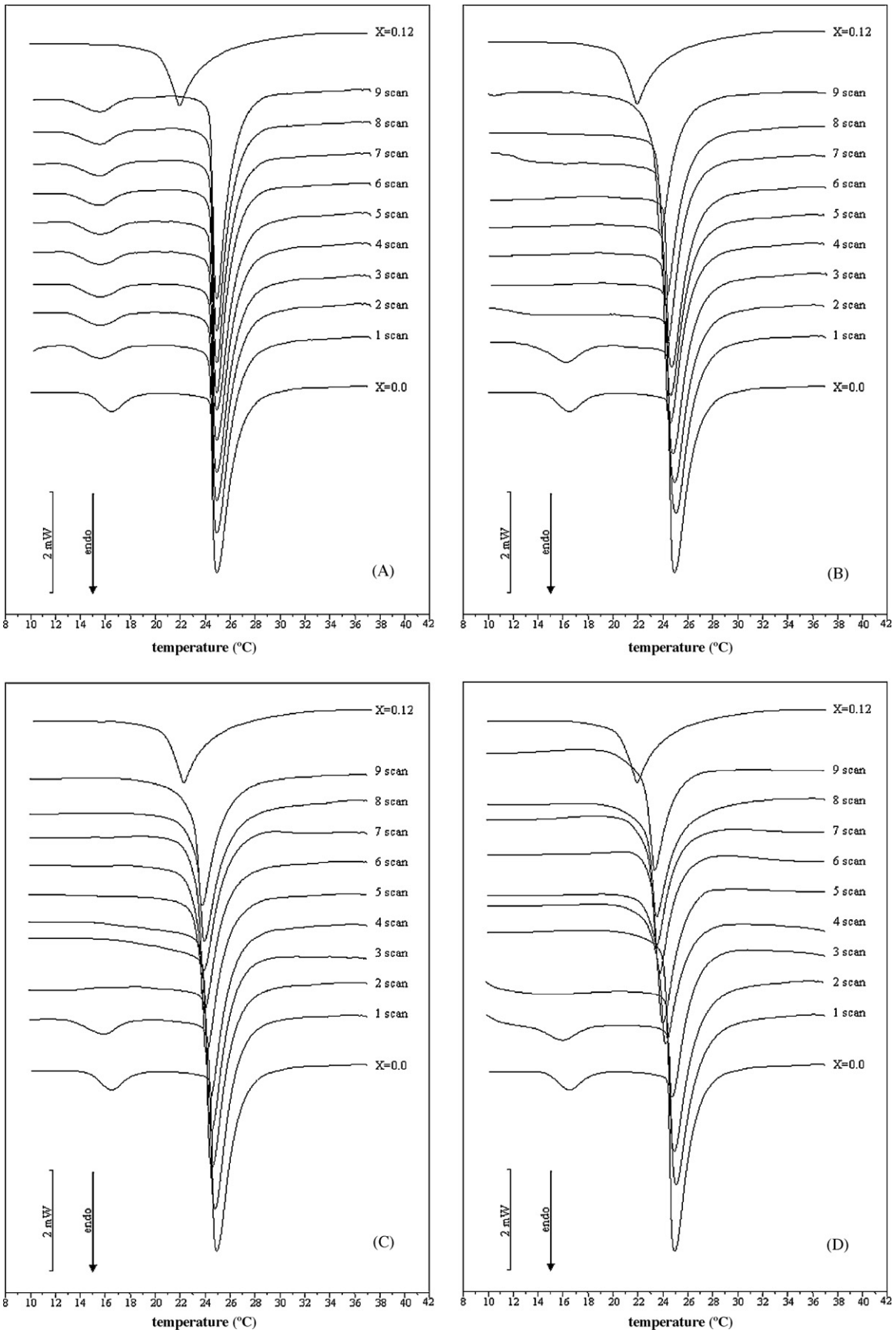

Fig. 3. Calorimetric curves, in heating mode, of DMPC MLV left in contact with TMS (A), TMS and β-CD at the following TMS/β-CD molar ratios 1:0.5 (B), 1:1 (C), 1:2 (D). Curve $X = 0.12$ belongs to DMPC MLV prepared in the presence of 0.12 molar fraction of TMS.

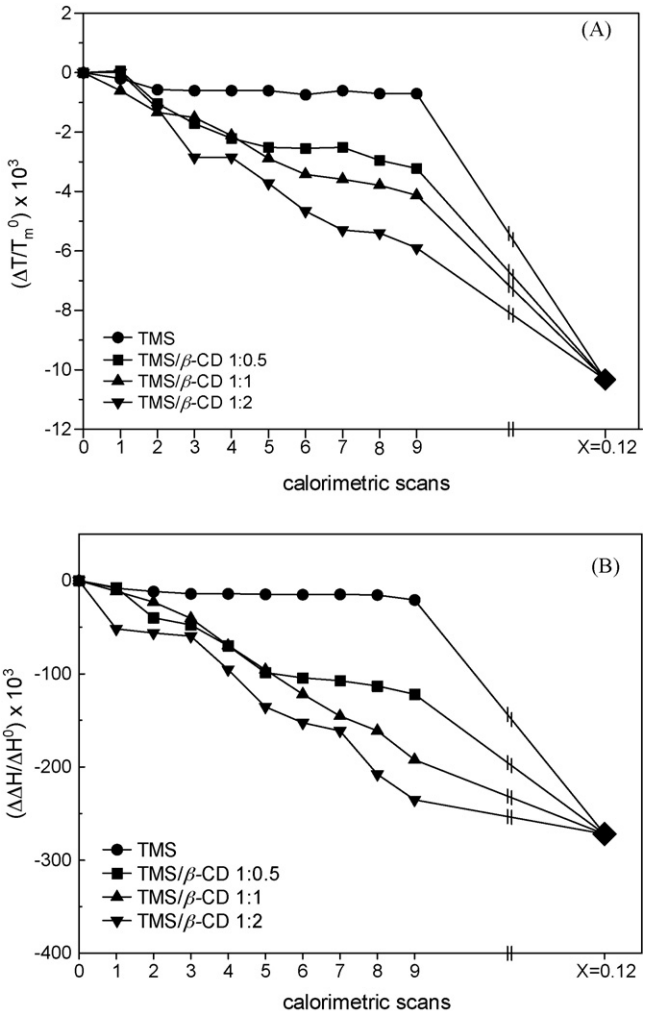

Fig. 4. (A) Transition temperature, as $\Delta T/T_m^0$, of DMPC MLV left in contact with TMS (0.12 molar fraction) or with TMS and β-CD, at different molar ratios, as a function of the calorimetric scans ($\Delta T = T_m - T_m^0$, where T_m^0 is the transition temperature of pure DMPC MLV and T_m is the transition temperature of DMPC MLV in the presence of TMS). (B) Enthalpy variation, as $\Delta\Delta H/\Delta H^0$, of DMPC MLV left in contact with TMS (0.12 molar fraction) or with TMS and β-CD, at different molar ratios, as a function of the calorimetric scans ($\Delta\Delta H = \Delta H - \Delta H^0$; where ΔH is the enthalpy variation of MLV which contain TMS and ΔH^0 is the enthalpy variation of DMPC MLV). $X = 0.12$ value represents the T_m (A) and ΔH (B) of DMPC MLV prepared in presence of 0.12 molar fraction of TMS and is considered as the maximum interaction between TMS and MLV.

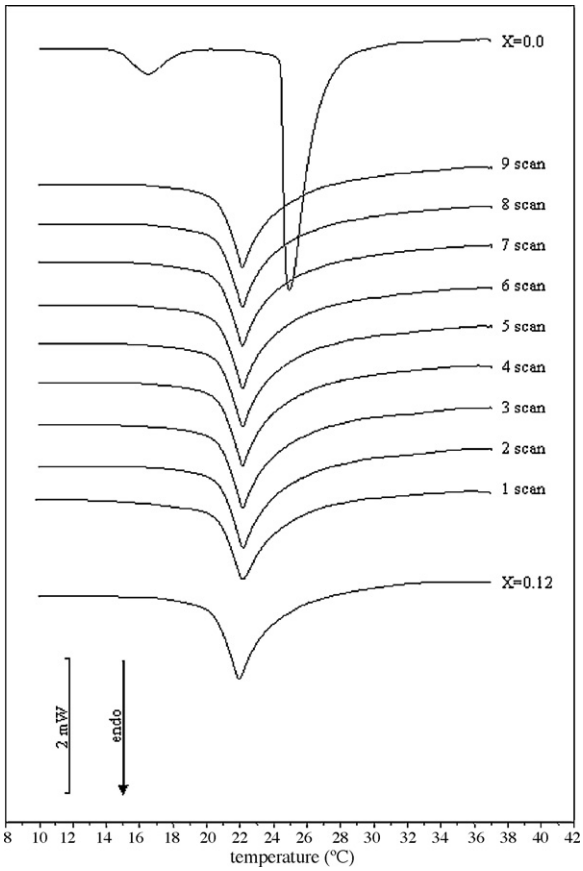

Fig. 5. Calorimetric curves, in heating mode, of TMS (0.12 molar fraction) loaded MLV left in contact with β-CD (TMS/β-CD molar ratio = 1:2). Curve $X = 0.12$ belongs to DMPC MLV prepared in the presence of 0.12 molar fraction of TMS. Curve $X = 0.0$ belongs to DMPC MLV.

variation neither in the shape nor in the position of the calorimetric curves with respect to that of DMPC MLV. When the β-CD (Fig. 3B–D) are present, as a general trend, TMS causes the disappearance of the pretransition peak starting from the second scan and the gradual broadening and shift of the main peak towards lower temperatures. We also reported the transition temperature, as $\Delta T/T_m^0$ (Fig. 4A) and the enthalpy variation, as $\Delta\Delta H/\Delta H^0$ (Fig. 4B) as a function of the calorimetric scans interesting considerations can be done. In the figure, $\Delta T = T_m - T_m^0$; where T_m is the transition temperature of MLV which contain TMS and T_m^0 is the transition temperature of DMPC MLV; $\Delta\Delta H = \Delta H - \Delta H^0$; where ΔH is the enthalpy variation of TMS containing MLV and ΔH^0 is the enthalpy variation of DMPC MLV; r is the transition temperature (panel A) or the enthalpy variation (panel B) of MLV prepared in the presence of a 0.12 molar fraction of TMS, as reported in liposomes preparation, and represent the maximum effect that TMS can induce on DMPC MLV at this molar fraction. TMS alone causes negligible variation on the transition temperature even at the ninth scan, whereas when β-CD are present a decrease of the transition temperature is observed. In particular, up to the fourth scan, no big differences as seen among the three TMS/β-CD molar ratios employed and a similar decrease of the transition temperature is observable; but for the successive scans the decrease of the transition temperature varies as a function of the β-CD amount; in fact, the bigger is the β-CD amount the more marked is the decrease. Similar profiles are attained when the enthalpy variation is considered. From these results it can be said that TMS alone does not interact with the MLV; this behaviour can be due to the lipophilic nature of TMS which does not permit the compound to dissolve in the aqueous medium surrounding the MLV, to get in contact with the MLV surface and, consequently, to be absorbed by the phospholipid bilayers. The decreases of the MLV transition temperature and of the associated enthalpy upon β-CD and TMS addition, clearly indicate that TMS is absorbed by the biomembrane model and interacts with the bilayers. Then, β-CD can form inclusion complexes with TMS acting as solubilizing agents for the compound. Recently, the formation of complexes between β-CD and trans-resveratrol, which is deeply related to TMS was demonstrated (Lu et al., 2009). This finding strengthens our hypothesis on the possibility that β-CD could form inclusion complexes with TMS. Moreover, the enhancement of the solubilization process depends on the amount of β-CD; in fact, the solubilization is more pronounced when the amount of β-CD is higher.

Once evidence of the improved absorption of TMS by MLV has been obtained, the stability of the MLV/TMS system and the ability of β-CD to extract TMS from MLV have been investigated. For this purpose kinetic experiments have been performed leav-

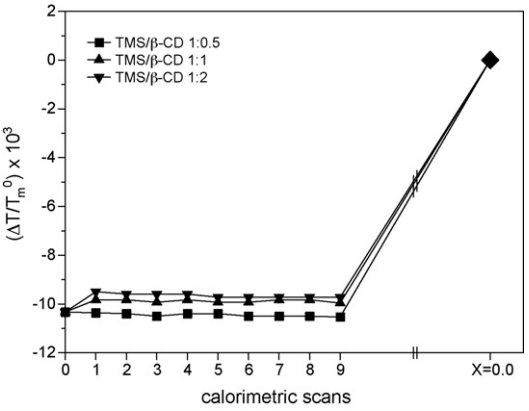

Fig. 6. Transition temperature, as $\Delta T/T_m^0$, of TMS (0.12 molar fraction) loaded MLV left in contact with β-CD (TMS/β-CD molar ratio = 1:2) as a function of the calorimetric scans ($\Delta T = T_m - T_m^0$, where T_m^0 is the transition temperature of pure DMPC MLV and T_m is the transition temperature of DMPC MLV in the presence of TMS). In the abscissa axis, the value at 0 is the transition temperature of DMPC MLV containing 0.12 molar fraction of TMS and the value $X = 0.0$ is the transition temperature of DMPC MLV and is the value to obtain if β-CD was able to extract TMS from the MLV.

ing TMS (0.12 molar fraction) loaded MLV in contact with β-CD (to have TMS/β-CD = 1:0.5, 1:1, 1:2, molar ratios) and submitting to calorimetric analysis. Due to the similarity of the calorimetric curves obtained, just those relative to TMS/β-CD = 1:2 molar ratio are shown in Fig. 5 and compared with the calorimetric curves of MLV containing a 0.12 molar fraction of TMS and of DMPC MLV. The latter is used as reference being the curve which should be obtained if the MLV/TMS was not stable and the β-CD extracted TMS from MLV. The calorimetric peak does not exhibit significant variation neither in shape nor in position and the curve of the DMPC MLV reference is never reached. Fig. 6 reports a comparison of the transition temperatures ($\Delta T/T_m^0$), as a function of the calorimetric scans. In the abscissa axis, the 0 value is the transition temperature of DMPC MLV containing 0.12 molar fraction of TMS, whereas the value $X = 0.0$ is the transition temperature of DMPC MLV (see Fig. 2) and it is the ideal value obtained if β-CD is able to extract all the TMS from the MLV. The transition temperature relative to the TMS/β-CD = 1:0.5 molar ratio does not change for all the calorimetric scans, whereas a very small increase is seen for TMS/β-CD = 1:1 and 1:2 molar ratios. Anyway the value $X = 0.0$ is quite far to be reached. This is a clear evidence of the stability of the MLV/TMS system and of the inability of β-CD to extract TMS from MLV.

Taking together our findings, we can say that TMS by itself, being hydrophobic and unable to pass through the aqueous medium, cannot be absorbed by MLV and hence cannot interact with the phospholipid bilayers. Furthermore, the presence of suitable concentrations of β-CD improves the MLV/TMS interaction. In fact, β-CD could encapsulate TMS and make it more suitable to diffuse in the aqueous medium, come in contact with the MLV surface and allow the absorption by the biomembrane models.

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