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ORIGINAL ARTICLE

# First generation newkome-type dendrimer as solubility enhancer of antitumor benzimidazole carbamate

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**Abstract** A first generation dendrimer was evaluated as solubility enhancer of the antitumor compound methyl (5-[propylthio]-1*H*-benzimidazol-2-yl) carbamate. The dendrimer possess carboxylic acid as terminal groups, which provide high water solubility and a low cytotoxic character. The drug-dendrimer association significantly increases active compound solubility in water, avoiding aggregation. The formulation is stable several weeks in a wide temperature range. The formation of Langmuir monolayers in air–water interface of dendrimer-active compound blends evinces the viability of the complex to generate films for surface-mediated drug delivery systems.

**Keywords** Biomaterials · Dendrimer · Host–guest association · Solubility · Langmuir monolayer

## Introduction

Compounds derived from benzimidazole possess a number of interesting therapeutic applications, including antimicrobial capability, activity against several viruses such as HIV, antiallergic, antioxidant, antihistaminic, antitubercular, antiulcer, anthelmintic, anticoagulant and anti-inflammatory capacity [1]. Recent research [2] have demonstrated that methyl 5-propylthio-1*H*-benzimidazole-2-yl carbamate (Albendazole, see Fig. 1a), commonly utilized as a broad spectrum anthelmintic agent [3], have a good potential as antitumoral agent. Its application in cancer therapy is under development [4]. This benzimidazole carbamate derivative is characterized by a high therapeutic index; nevertheless its clinical applications are restricted due to their poor solubility, and adsorption problems [5].

The vehiculization of drugs using a variety of carriers has emerged as the workhorse solution to manage poor biodistribution and stability of bare therapeutics drugs [6, 7]. Previous studies showed that complexation of ABZ with povidone and cyclodextrins increases their solubility, improving its bioavailability as well [8, 9]. Also Zhao et al. demonstrated that encapsulation of ABZ in cucurbit[*n*]uril significantly increased its aqueous solubility, without significantly affecting the in vitro cytotoxicity against a range of cancer cell lines [10].

Dendrimers are a specific class of polymers, with well-defined structures suitable for drug solubilization applications [11]. They are characterized by a precise architecture, high level of control of branching points, surface functionalization and low polydispersity [12]. Due to the dendrimeŕs properties, these branched polymers have emerged as one of the most promising innovative vehicles for different therapeutic agents [13–15].

In a previous work we investigated the effect of commercial polyamidoamine (PAMAM) dendrimers on the aqueous solubility of the hydrophobic drug ABZ. Different generations (G) of PAMAM dendrimers with amine terminal groups (G3), hydroxyl terminal groups (G3OH) and with carboxylate terminal groups (G2.5 and G3.5) were evaluated as solubility enhancers. All these polymeric

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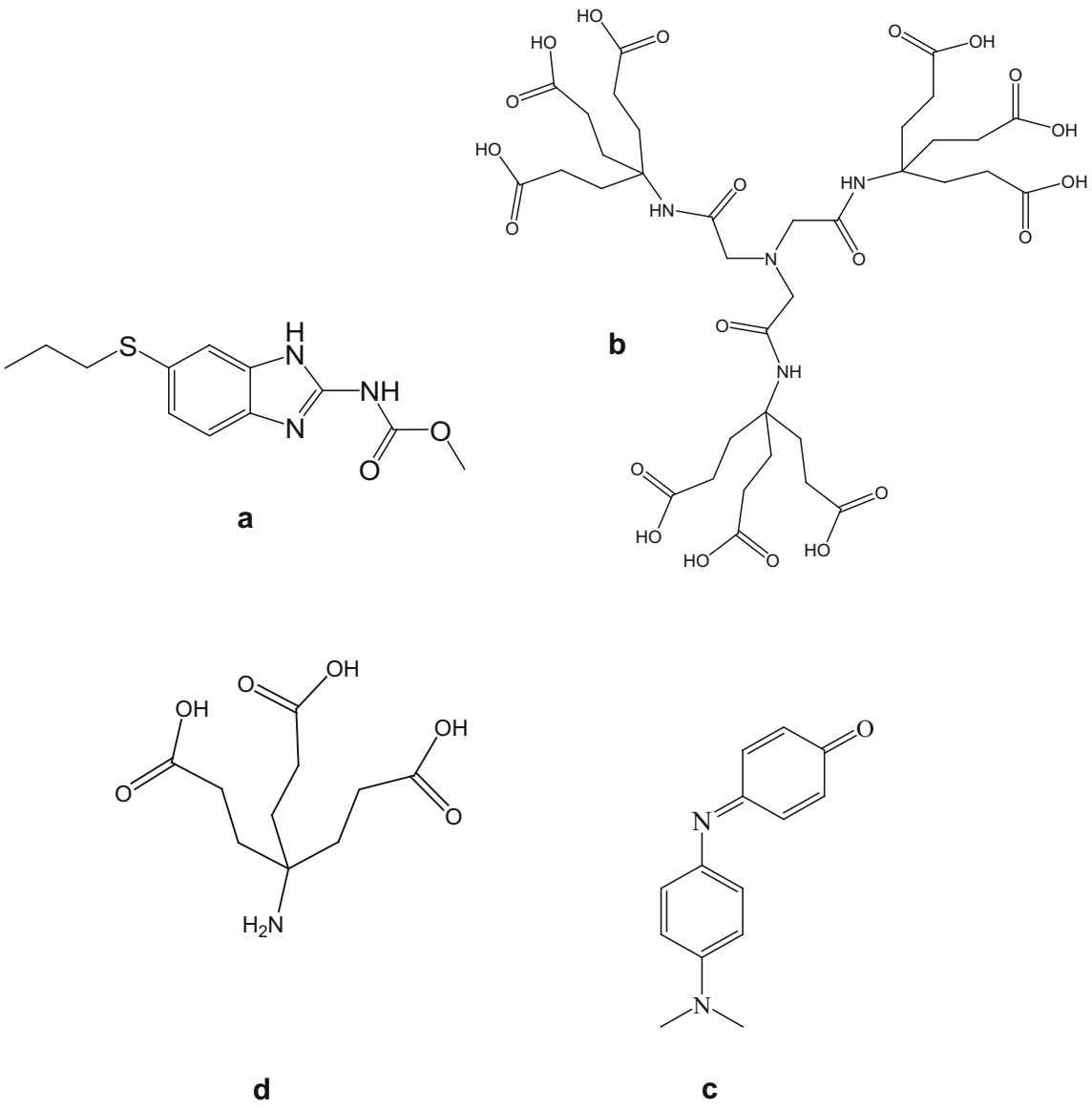


**Fig. 1** Chemical structure of methyl (5-[propylthio]-1*H*-benzimidazol-2-yl) carbamate (ABZ) (**a**), first generation dendrimer (**b**), phenol blue (**c**) and tris (propionic acid) aminomethane (**d**)

structures have shown good capacity for to increase the solubility of ABZ [16]. The difference as solubility enhancer of the diverse PAMAM dendrimers was attributed to the nature of the ABZ-dendrimer interactions, which depend on the identity of the surface functional groups. The dendrimer that achieved higher increase in ABZ solubility was amine terminal dendrimer G3, which unfortunately is the more cytotoxic due to their surface cationic groups [17]. As it was already reported, dendrimers with cationic groups at the surface show adequate drug delivery efficacy, but their cytotoxicity is still a problem that limits the clinical applications of drug formulations holding cationic dendrimers [18]. On the other hand vehicles with anionic and neutral surface groups were found to be substantially less cytotoxic than the cationic ones. Furthermore, lower generation dendrimers tend to exhibit considerably lower cytotoxicity than the higher generations [19, 20].

In this work we evaluated the enhancement of ABZ solubility using a Newkome-type first generation dendrimer, **D1** (Fig. 1b). This dendrimer possess carboxylic acid as terminal groups, which provide high water solubility and a low cytotoxic character. Also it holds suitable capacity for association with lipophilic compounds [21]. The performance of the **D1** dendrimer as solubility enhancer of the benzimidazole carbamate derivative was evaluated by UV–Vis spectroscopic. The dendrimer-drug association stability along several weeks and at different





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temperatures was also analyzed. In addition, in order to obtain a proper description of the guest–host interaction, we investigated the polarity and accessibility of the first generation dendrimer using a probe molecule (phenol blue, Fig. 1c). Also, the viability of this dendrimer-drug complex to generate composite monomolecular monolayers was also examined, in order to evaluate the potential development of the system for surface-mediated drug delivery.

## Materials and methods

### Materials

**D1** dendrimer was synthesized, purified and characterized using the methodology described by Fernandez et al. [21]. Phenol blue and methyl (5-[propylthio]-1*H*-benzimidazol-2-yl) carbamate ABZ (Sigma-Aldrich) were used without further purification. The organic solvents (methanol, propanol, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, acetonitrile, benzene and tributylamine) were obtained from Sintorgan in HPLC quality and used without further purification. Deionized water was obtained from Elga Classic equipment (resistivity of 18 MΩ cm). The UV cut-off point of the solvents in a UV cell of 10 mm against air was used as purity criteria. UV visible spectroscopic measurements were performed using a Shimadzu UV 2401PC spectrofotometer at 20.0 ± 0.2 °C.

### Drug solubilization mediated by dendrimer

Stock solutions of drug $1.0 \times 10^{-3}$ M were prepared dissolving the guest in methanol, and stored in darkness. Appropriate amounts of drug stock solution were transferred into 5 mL volumetric flasks, the solvent evaporated off under nitrogen atmosphere and the samples were diluted to the appropriate volume with aqueous dendrimer solution $1.0 \times 10^{-4}$ M. The sample were sonicated for 2 h, and allowed to equilibrate in darkness overnight. The sonication bath temperature was kept constant at 36 °C. A small amount of drug precipitated from solution and was removed via filtration through a 0.45 μm Millipore membrane. The same procedure was carried out with the pure drug, in the absence of dendrimer, in order to determine its solubility in identical experimental conditions.

### Guest-D1 dendrimer interaction analysis

Stock solution $3.0 \times 10^{-3}$ M of phenol blue was prepared dissolving the dye in methanol and stored in the darkness at room temperature. Appropriate amounts of phenol blue stock solution were transferred into 5 mL volumetric flasks, and the solvent evaporated off under nitrogen atmosphere. The samples were diluted at $1.0 \times 10^{-5}$ M with either; tributylamine, aqueous solutions of branched molecule tris (propionic acid) aminomethane (Fig. 1d), pure water and $1.0 \times 10^{-4}$ M aqueous dendrimer solution. All samples were sonicated for 10 min to facilitate solubilization of the dye and stored at room temperature in the dark.

### Stability testing

In order to study the stability of the system over time at room temperature, we analyze the spectral characteristics of solutions containing the drug-dendrimer complex for a period of 2 months. On the other hand, freshly prepared drug-dendrimer solutions were thermostated at different temperatures covering a range between 15 and 40 °C. After reaching thermal equilibrium, solutions were filtered through a 0.45 μm Millipore membrane and the absorption spectrum was determined.

### Hemolytic study of D1 dendrimer-ABZ active compound formulation

From human blood collected at the UNRC Health Center, a 2 % w/v red blood cell (RBC) solution was prepared and centrifuged at 1500 rpm for 10 min at 4 °C. The plasma supernatant was removed and the erythrocytes were suspended in ice cold PBS. The cells were again centrifuged at 1500 rpm for 10 min at 4 °C. This procedure was repeated two more times to ensure the removal of any released hemoglobin. Once the supernatant was removed after the last wash, the cells were suspended in PBS to get a 2 % w/v RBC solution. The solutions were also prepared in PBS via serial solutions for each concentration and incubated for 1 or 24 h at 37 °C. Complete hemolysis was attained using neat water yielding the 100 % control value (positive control). After incubation, the tubes were centrifuged and the supernatants were transferred to new tubes. The release of hemoglobin was determined by spectrophotometric analysis of the supernatant at 414 nm. Results were expressed as the amount of hemoglobin release induced by the conjugates as a percentage of the total.

### Dynamic scattering measurements

The formation of aggregates in solution was determined by dynamic light scattering (DLS) using a Malvern 4700 goniometer and 7132 correlator, with an argon-ion laser operating at 488 nm at a temperature of 25 °C. All measurements were done in triplicate, at the scattering angle of 90° and CONTIN analysis was used to obtain the size distribution of the aggregates.





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## Langmuir films

Measurements were carried out using a Langmuir–Blodgett (LB) trough (Model 611, Nima Technology). The surface pressure was measured using the Wilhelmy plate method. Deionized water was used as subphase. Chloroform solution ($6 \times 10^{-4}$ M, 50 μL) of dendrimer were carefully spread on the water surface and 10 min were allowed to pass before measurements in order to permit evaporation of the solvent. For the experiments with solution containing drug-dendrimer mixture was used chloroform solution of both molecules in a molar ration 4:1 ($6 \times 10^{-4}$ M of dendrimer and $2.4 \times 10^{-3}$ M of drug). In all the experiments the subphase temperature was kept constant at 25 °C. Barrier speed was 50 $cm^2$/min for compression and expansion.

## Results and discussion

### Drug solubilization mediated by dendrimer

As it was already mentioned, ABZ exhibit significant antitumor activity [22] but pour water solubility. Therefore, their association with a water soluble dendrimer as carrier could allow optimizing their biodisponibility and therapeutic applications.

Changes in the guest solubility were followed by the UV–Vis absorption spectra of ABZ in different concentrations of aqueous **D1** dendrimer solutions (Fig. 2, the spectrum of ABZ in pure water is also included for reference). The **D1** dendrimer concentration was varied between

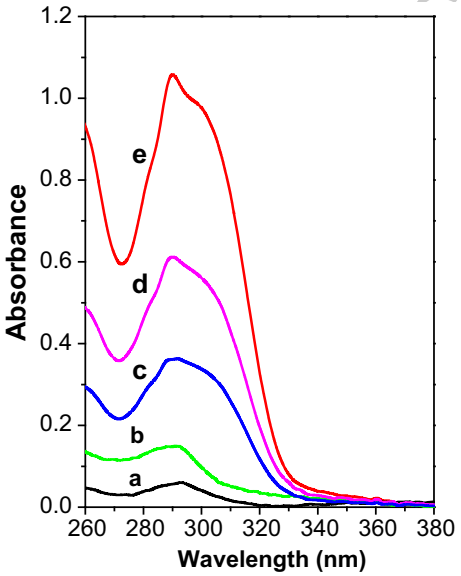
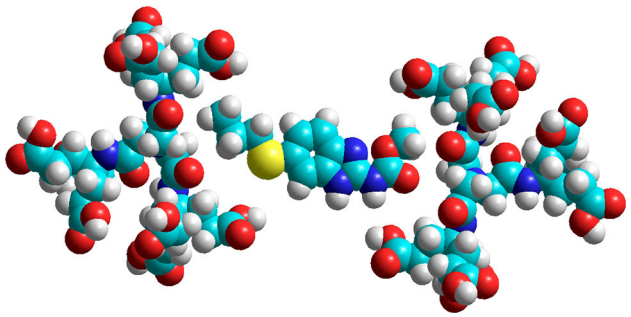



**Fig. 2** Electronic absorption spectra of ABZ in water *a* and in aqueous solution of different concentrations of **D1** dendrimer *b–e* $5.0 \times 10^{-6}$; $1.0 \times 10^{-5}$; $5.0 \times 10^{-5}$ and $1.0 \times 10^{-4}$ M, respectively



**Scheme 1** Schematic overview of ABZ—**D1** association

$5.0 \times 10^{-6}$ and $1.0 \times 10^{-4}$ M. ABZ was added in excess of its aqueous solubility limit ($2.4 \times 10^{-6}$ M) [5] allowing to observe the solubility improvement. It can be observed in Fig. 2 that as **D1** concentration increases, a concomitant enhancement in the ABZ solubility is obtained ([**D1**]/[ABZ] (molar) = $0/2.4 \times 10^{-6}$; $5.0 \times 10^{-6}/6.0 \times 10^{-1}$, $6.0 \times 10^{-5}/1.4 \times 10^{-5}$, $5.0 \times 10^{-5}/2.4 \times 10^{-1}$, $5.0 \times 10^{-4}/4.2 \times 10^{-5}$). Thus, an increase of approximately 20-folds in the ABZ solubility was obtained in $1.0 \times 10^{-4}$ M dendrimer aqueous solution, indicating the existence of dendrimer-therapeutic compound association.

On the other hand, it is known that compounds which exhibit poor aqueous solubility, as ABZ, have tendency to form aggregates, often with size vastly superior to that of the pure drug. Aggregate formation is an important aspect to consider when the studied compound has biological activity. The activity, pharmacodynamic and pharmacokinetic of aggregate could be drastically different when compared with the free drug [23]. To monitor the presence of aggregates, pure drug and drug-dendrimer complex aqueous solutions were studied by DLS. The aqueous solution of ABZ (in its apparent solubility limit, $2.4 \times 10^{-6}$ M) shows the presence of aggregates of average size 300 nm and a polydispersion index of 0.46. In contrast, light scattering is absent in dendrimer solutions ($1 \times 10^{-4}$ M), demonstrating the formation of a guest–host association, which is schematically represent in Scheme 1. In conclusion, in saturated aqueous solution, ABZ is self-associated, even after being subjected to sonication and filtration. The presence of dendrimer, however, increases the ABZ solubility and prevents aggregation.

### Guest-D1 dendrimer interaction analysis

In order to assess the capability of **D1** dendrimer for association with hydrophobic guests like ABZ, the polarity and accessibility of dendrimeric microenvironments were investigated using phenol blue (Fig. 1c) as spectroscopic molecular probe. Often spectrophotometric probe techniques provide realistic views of macromolecular media in fluid solution [24]. Phenol blue has been previously used as probe by Richter-





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Egger and coworkers to study poliamidoamine and polipropilenamine dendrimers with modified cores with excellent results [25]. The physical and spectroscopic absorption properties of phenol blue have been well characterized [26, 27] and the dye is believed to exist solely as neutral quinoneimine in both, protic and aprotic solvents of varying polarities. The combination of specific solvatochromic absorption behavior and his relatively small size (similar to ABZ) qualify phenol blue as an appropriate probe for this study.

Absorption spectra of phenol blue in different media that mimic the microenvironments that can be found in **D1** dendrimer water solutions were examined in order to determine the dyés location distribution. Thus, solutions of phenol blue in water, tributylamine, and **D1** dendrimer aqueous solutions were prepared and their absorption spectra recorded. In addition, aqueous samples of phenol blue containing $3.0 \times 10^{-4}$ M of tris (propionic acid) aminomethane (TPA, Fig. 1d) were also analyzed. At this concentration the solution possess the same number of TPA groups present in $1.0 \times 10^{-4}$ M of **D1** dendrimer in water, mimicking their surface groups. In the same way, tributhylamine was used to mimic dendrimeric central core. Electronic absorption spectra of phenol blue in the different analyzed media are shown in Fig. 3. The effect of the diverse environments is clearly evidenced by the shifts in phenol blue spectra. Absorption band of the dye shifts to shorter wavelengths as the solvent polarity decrease [25] ($\lambda_{max}$ range from 659 nm in water to 555 nm in tributhylamine). In water solution with TPA, phenol blue absorption spectra possess a $\lambda_{max}$ at 568 nm, similar to the one obtained in low polarity media. On the other hand, phenol blue spectrum in **D1** dendrimer solution clearly shows a wide and asymmetric absorption band, with $\lambda_{max}$ at 562 nm, close to the observed in pure tributhylamine and TPA solutions, and a shoulder around 668 nm. These effects indicate the existence of two different dye populations in the presence of **D1** dendrimer. The main part of phenol blue is surrounded by a non-polar microenvironment defined by the dendrimer branches, as it is indicated by the large absorbance at short wavelength. The remaining dye is located in a predominantly aqueous polar environment. Thus, the studies with phenol blue indicate that the **D1** dendrimer generate a low polarity environment where lipophilic molecules can be hosted. This allows us to propose that the enhanced solubility of ABZ in the presence of **D1** dendrimer could be due to the association with **D1** lipophilic environment. This assumption is also supported by the analysis of the absorption spectra of ABZ in different solvents. Figure 4 shows that as the solvent polarity decrease the ABZ electronic absorption spectra move to higher energy, as was already reported [16]. Consequently the shift observed in the absorption band of ABZ in dendrimer containing water solution indicates a decrease in microenvironment polarity around ABZ with respect to pure water. However, the observed enhancement in drug solubility also could involve the existence of drug-dendrimer specific interactions, in addition to the lipophilic ones. It is possible than hydrogen bonds between the active compound and the dendrimer facilitate the association of this host–guest system, due to the presence of donor and acceptor hydrogen bonding groups in both, ABZ and **D1** dendrimer structures (Fig. 1) [16, 21].

## Stability testing and hemolytic potential of dendrimeric system

In order to infer conditions suitable for drug-dendrimer potential formulation storage, we evaluated the stability of

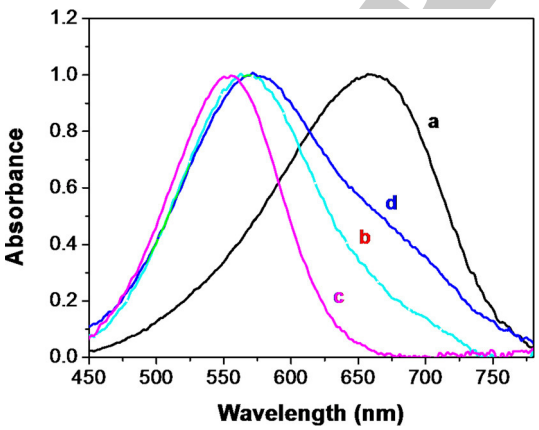


**Fig. 3** Normalized electronic absorption spectra of phenol blue [$1.0 \times 10^{-5}$ M] in: *a* water; *b* $3.0 \times 10^{-4}$ M aqueous solution of tris (propionic acid) aminomethane; *c* tributylamine and *d* $1.0 \times 10^{-4}$ M aqueous solution of D1 dendrimer

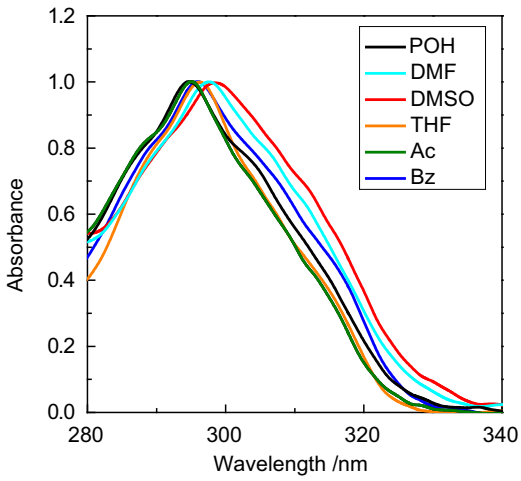


**Fig. 4** Normalized electronic absorption spectra of ABZ in solvents with different polarity: propanol (POH), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), acetonitrile (Ac) and benzene (Bz)





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the guest–host association. Samples were prepared and analyzed initially and periodically up-to 10 weeks checking for any precipitation, turbidity, crystallization, color change, and drug leakage. No change in turbidity, color, and consistency was noticed in formulations. Absence of drug leakage from the formulation during storage was determined monitoring drug content spectrophotometrically. No change was observed in absorption spectra of the drug-dendrimer system. Also, studies were conducted to evaluate the temperature variation effect in the guest-dendrimer association, covering a range between 15 and 40 °C. As is shown in Fig. 5, absorbance of ABZ in aqueous solution of **D1** dendrimer at $\lambda = 298$ nm does not present significant alterations with temperature variation. The system was found to be sufficiently stable even at elevated temperatures up to 40 °C.

On the other hand, as was already mentioned, the newkome type dendrimer present null or very low hemolytic activity [21]. The studies showed that **D1** dendrimer is non-hemolytic up to concentration of $2 \times 10^{-3}$ M. In comparison, PAMAM G3 dendrimer present hemolytic activity, even at low concentrations [17]. We conducted cytotoxicity study of the whole formulation (D1 dendrimer-ABZ active compound) and the obtained results indicate than the system is non hemolytic (Fig. 6), and does not show time-dependent hemolysis. RBC lysis was not observed even at [**D1**]/[ABZ] $1.0 \times 10^{-4}$/$4.8 \times 10^{-5}$ molar concentrations for 24 h (Fig. 6). This fact indicates that the host–guest formulation is able for to be used as an active drug carrier.

## D1 dendrimer-ABZ composite Langmuir films

As already mentioned, it is well know the applicability of dendrimers as drug carriers in solution. Additionally, in the last years, application of dendrimers in surface-mediated drug delivery has been extensively investigated [20, 28, 29]. Polymer containing films can act as reservoir for active therapeutic cargo, allowing controlled release of therapeutic molecules. However, to make possible functional formulations, the association between carriers and active compounds must be present in the films, without phase segregation. This drug-dendrimer association at molecular layer levels (two dimensional solid) can be studied by Langmuir technique. This method can help to access valuable information about the behavior of a dendrimer-drug film in air–water interface. Also allows understanding the general principles that determine the molecular conformation in the film [30]. Thus, surface pressure-area ($\pi - A$) Langmuir isotherms can be used as suitable tool to analyze binding interactions and the affinity among molecule in **D1** dendrimer-ABZ association at monomolecular film level [31, 32].

In our case, first the capability of **D1** dendrimer to form stable monolayers at the air–water interface was studied by the corresponding $\pi - A$ isotherms. Line (a) in Fig. 7 shows a continuous increase in surface pressure as the available area per molecule decreases. Plateaus areas are not observed, indicating the absence of phase transitions. These results allow us to infer that dendrimeric structure is gradually accommodated in the interface, without display conformational changes during compression, showing a direct transition from the gaseous phase to the solid phase. Moreover it can be observed a large value for the collapse pressure (about 30 mN/m), which indicates that the molecules suspended on the interface can resist high compression generating a stable dendrimeric monolayer [33].

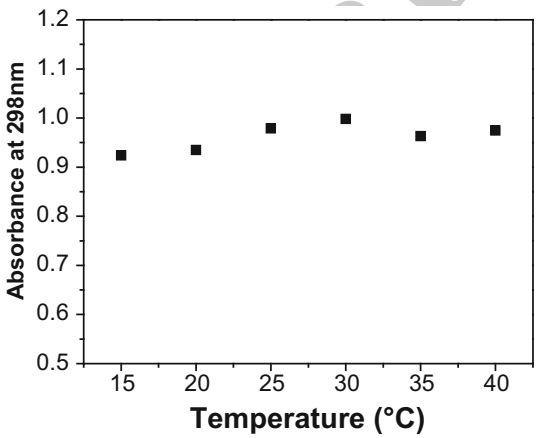


**Fig. 5** Absorbance of ABZ at $\lambda = 298$ nm as function of temperature in aqueous solution of dendrimer. [D1] $= 1.0 \times 10^{-4}$ M

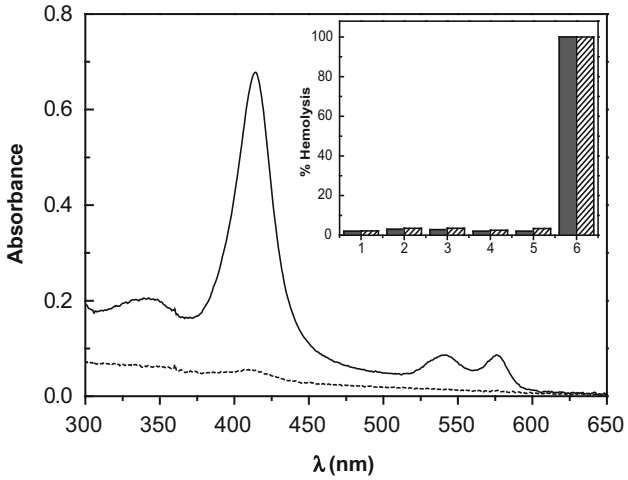


**Fig. 6** Absorption spectra of hemoglobin in red blood cells treated with (*solid lines*) PBS and (*dashed lines*) double-distilled water. *Inset*: Hemotoxicity of **D1** dendrimer-ABZ formulation at 1 and 24 h. Red blood cells 2 % w/v treated with: *1* PBS; *2* ABZ in PBS; *3–5* **D1** dendrimer-ABZ formulation [**D1**]/[ABZ] $1.0 \times 10^{-5}$/$1.4 \times 10^{-5}$; $5.0 \times 10^{-5}$/$2.4 \times 10^{-5}$; $1.0 \times 10^{-4}$/$4.2 \times 10^{-5}$ molar respectively. *6* Red blood cells 2 % w/v treated with double-distilled water







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When the monolayer is in the two dimensional solid phase, the molecules are relatively well oriented and closely packed. The zero-pressure molecular area ($A_0$) can be obtained extrapolating the slope of the solid phase of the $\pi - A$ isotherm. This parameter provides quantitative information about the molecular dimensions and shape of the dendrimer in the interface. The molecular area obtained for **D1** dendrimer in monolayer was $A_0 = 220$ Å$^2$. On the other hand, using semiempirical method calculation (AM1 at HyperChem Software) the cross-section area obtained for **D1** exhibit a value of $A_{cal} = 260$ Å$^2$, which is similar than that obtained experimentally. This fact suggests that throughout the monolayer formation, **D1** molecules suffer not or low domain aggregation, occupying an area comparable than the theoretically expected. All the results allow considering that the dendrimer is located at the interface with terminal acid groups directed toward the water, resembling a spider that rests on it. Thus, the capability of the **D1** dendrimer to form stable monolayers, together with its ability to associate with small molecules, allows analyzing the association between the carrier and therapeutic compounds in monomolecular films. The dendrimer could act as a scaffold able to interact with a drug unfit to form stable monolayers alone, like ABZ. In Fig. 7 line (b) shows the surface pressure-area isotherm obtained when a **D1** dendrimer-ABZ mixture (molar ration 1:4) is spread on the water surface and compressed. The results indicate that in presence of ABZ, **D1** dendrimer preserves its ability to form stable monolayer. However, the presence of ABZ produces a shifted isotherm toward larger areas, without changing the shape of the curve or the value of the collapse pressure. The molecular area at zero pressure determined for the drug-dendrimer system yielded a value of 250 Å$^2$, superior to that obtained on the isotherm of pure dendrimer. These results indicate that the active compound associated with dendrimer monolayer increasing the effective area occupied on the interface. This area increment of around 30 Å$^2$ reasonably fits with the expected for the four ABZ molecules. According to semiempirical calculations the cross-section area obtained for each ABZ molecule is 9 Å$^2$. It should be remarked that pure ABZ spread over water does not allow obtaining molecular monolayers, producing instead visible aggregates islands just after solvent evaporation. Thus, the results clearly indicate that the **D1** dendrimer-ABZ association at molecular level prevents the active drug aggregation, analogous to the observed in homogeneous media. These facts clearly indicate that **D1** dendrimer could be used as potential carrier for the anti-tumoral compound in both; solution and surface-mediated drug delivery systems.

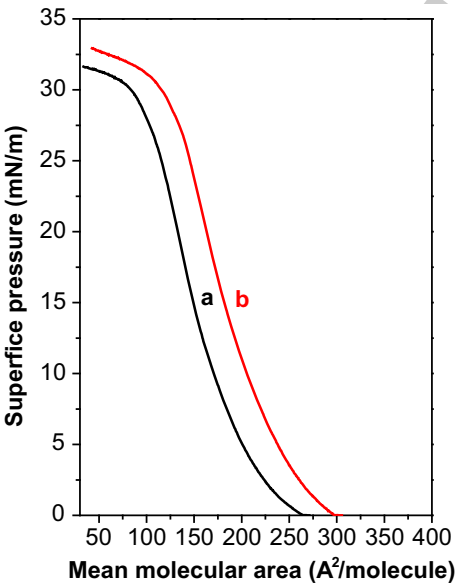


**Fig. 7** Surface pressure-molecular area isotherms in the air/water interface at 25 °C of *a* D1 dendrimer and *b* ABZ/D1 dendrimer mixture (4/1)

On the other hand, in order to analyze the evolution of the monolayers on water surface, we performed successive compression-expansion cycles and isobaric creep measurements. Figure 8a shows the hysteresis curves for **D1**-dendrimer monolayer. As can be seen, each cycle shows a shift of the curve towards smaller area, but this phenomenon does not alter the shape of the isotherm, which allows us to suggest that the conformation of the dendrimer molecules on the water surface is similar after each compression. The decrease in specific area per molecule after the compression/expansion cycle is likely due to reorganization of molecules in the monolayer. Because of the flexibility of dendrimeric branches, the molecules can interpenetrate each other, changing their conformations to minimize free energy at the air–water interface. [34]. A similar result is obtained when **D1** dendrimer-ABZ mixture (molar ration 1:4) monolayer is successively compressed and expanded (Fig. 8b), showing that the presence of ABZ does not alters the dendrimer monolayer stability. However, when a constant surface pressure (20 mN/m) is maintained in both kinds of monolayers (dendrimer alone and dendrimer-ABZ mixture) it is observed that the occupied areas continuously decrease (Fig. 9). It is likely that once formed the monolayer, and subjected to high pressure, the dendrimer molecules and dendrimer ABZ mixture dissolve into the water sub-phase, causing the diminution in the areas covered by the monomolecular films. As was observed, the **D1**-ABZ mixture in two dimensional solid slowly dissolves into water subphase, instead pure ABZ remains as floating islands. Thus, it is not unreasonable to propose the study of this dendrimeric system as active therapeutic reservoir for surface-mediated drug delivery.





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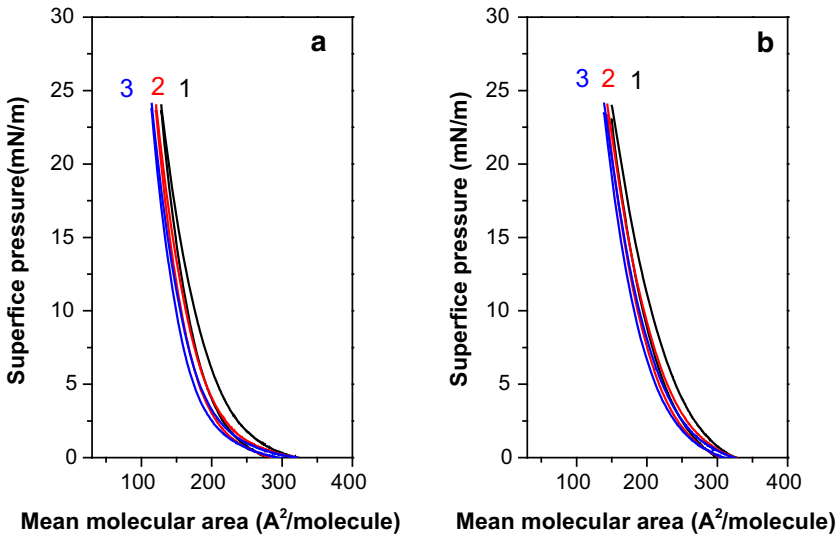


**Fig. 8** Hysteresis cycles showing the surface pressure during successive compressions and expansions of D1 dendrimer (*left*) and mixture ABZ-D1 dendrimer (4/1) (*right*) at 25 °C. First cycle (*1*), second cycle (*2*) and third cycle (*3*)

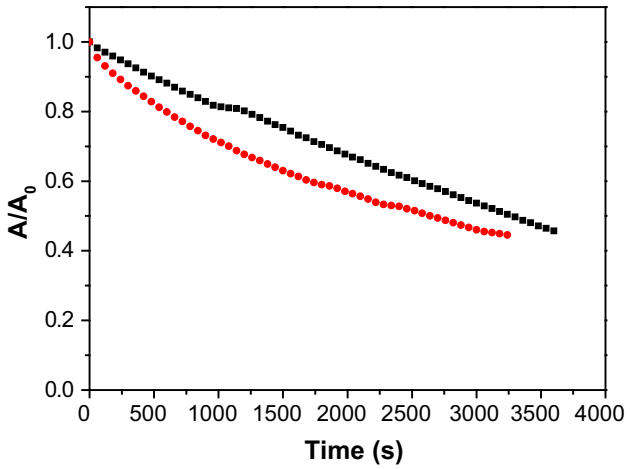


**Fig. 9** Isobaric creep measurements of D1 dendrimer (*filled square*) and mixture ABZ-D1 dendrimer (4/1) films (*filled circle*) at 20 mN/m for 1 h

## Conclusion

A dendrimer carrier-therapeutic agent association allowed the solubility enhancement of the antitumor compound methyl (5-[propylthio]-1*H*-benzimidazol-2-yl) carbamate. The drug-dendrimer association prevents the aggregation of the active compound, as probed by light scattering analysis. Dendrimer-guest interaction characterization, through the uses of a solvatochromic probe molecule, allowed us to propose that both, hidrofobicity and hydrogen bond specific interaction could be the possible mechanism for the solubility enhancement, generating a complex that is stable for several weeks in a wide temperature range (15–45 °C). Also, we demonstrated that **D1** dendrimer is able to form stable Langmuir monolayers in the air–water interface, even if it is spread associated with the active drug. These results highlight the potential of the carboxyl-terminated dendrimers for drug encapsulation and evince the viability of this dendrimer-drug complex to generate composite layers to develop system for surface-mediated drug delivery.

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