 DOI: 10.1002/masy.200900078

Simulation of Itraconazole Encapsulation by Novel Biocampatible Dendritic Compounds

*Igor Elkin, Patrice Hildgen**

Summary: To enhance the dissolution rate of itraconazole, the novel macromolecular biocompatible dendritic compounds were selected. The possible drug encapsulation was evaluated by the calculated difference between potential energies of the individual dendrimers and structures having one itraconazole molecule near the dendrimer core. The structures with the decanediol spacers and with the core presented by 1,2,3,4-butanetetracarboxylic acid demonstrated better energetic effects to be good candidates as a drug delivery carrier for itraconazole pharmaceutical applications. Additional simulations with the less bulky modeling structures with different cores, using molecular dynamic procedure, allowed us to obtain the best results with the tetracarboxy benzene core.

Keywords: biocompatibility; dendrimer; encapsulation; itraconazole; simulation

Introduction

Itraconazole (**1**), invented in 1980, is an effective synthetic triazole antifungal agent that inhibits the synthesis of ergosterol, essential component of the fungal cell membrane. However, the solubility in water and, hence, the bioavailability of this compound are extremely low, reducing its therapeutic application.[1,2] Recent studies show that some dendrimers can act as potential carriers for small guest molecules and, consequently, as drug delivery vehicles. The presence of ester and polyethyleneoxid groups in dendrimer structures reveals the marked importance for better biocompatibility.[3] Moreover, theoretical simulation methods can provide with important information on the organization of dendrimer-guest molecule associates.[4]

The aim of the current work is to complete our synthesis experiments[5] by investigating the influence of the dendrimer tetrafunctional core and spacer structures on potential itraconazole encapsulation capacity. In addition, we are also interested in finding a reliable and computationally-inexpensive method to accurately predict the encapsulation process in dendrimers dependent on their architectures.

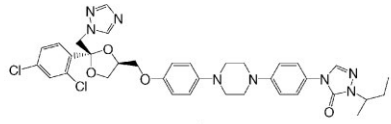
Methodology

The itraconazole encapsulation by the proposed dendrimers (**2**) was evaluated by the difference between calculated potential energies of the optimized individual (**2**) (E_D) and (**1**) (E_I) structures and the system having (**2**) and one molecule of (**1**) near (1.5 Å) the dendrimer core ($E_{D\text{-}I}$). This energetic difference ($\Delta E_{D\text{-}I}$) is expressed as: $\Delta E_{D\text{-}I} = E_I + E_D - E_{D\text{-}I}$ (kcal/mol). Thus, the higher the value of this criterion ($\Delta E_{D\text{-}I}$), the more effective is itraconazole encapsulation. As a geometry optimization simulation procedure we used Molecular Mechanics Force Field (Amber3) method with Polak-Ribiere algorithm and the root mean square (RMS) gradient of $\leq 1{\cdot}10^{-3}$ kcal/(Å mol). The molecular dynamic procedure (MD) (heat time: 0.5 ps, run time: 1 ps, cool time: 0.5 ps, step size: 0.001 ps, starting temperature: 0K, simulation temperature: 300K, final

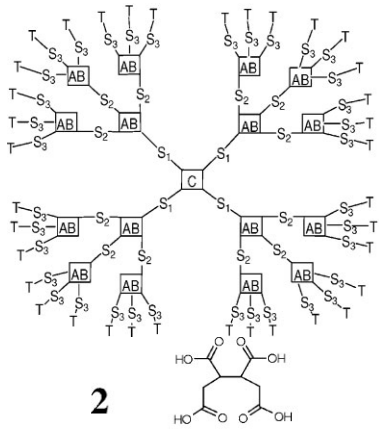
Faculté de Pharmacie, Université de Montréal, Québec, H3C 3J7, Canada
Fax: (+1) 514 343 6871;
E-mail: patrice.hildgen@umontreal.ca

temperature: 0K, temperature step: 10K) was adopted for calculations as follows: geometry optimization – molecular dynamic procedure – geometry optimization.[6] All the calculations were made with the HyperChem™ 8.0.4 package.[7]

mer (**2**, C-I) molecule and, lastly, for the ''dendrimer-itraconazole'' system (1:1). During our work, we changed the nature of spacers S_1 and S_2. In case of S_1 spacer absence, the core and branching agent were coupled by ester bond directly without

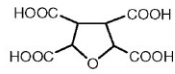


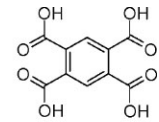
1



2

$S_{1\text{-}3}$-spacers: tetraethyleneglycol (TEG), 1,10-decanediol (DD),
T- terminal group: -CH_2-CH_2-CH_2-OH,
AB- branching agent: C(-CH_2-O-CO-CH_2-CH_2-COOH)$_4$
C- core :





C-I C-II C-III

Results and Discussion

First of all, we encapsulated itraconazole by our whole dendrimer structure (**2**) with the core C-I *in vacuo*. To achieve this, we performed geometry optimization procedures separately for 1 individual itraconazole molecule (**1**), for 1 individual dendrimer branching agent succinic fragments. Table 1 reports the values of potential energies of these compounds obtained after the geometry optimizations and also the values of criterion $\Delta E_{D\text{-}I}$, calculated as described above. According to the obtained data (Table 1), structures with spacer combinations $S_1 = DD$, $S_2 = DD$, $S_1 = 0$, $S_2 = DD$,

Table 1.
Simulation results for the dendrimers (**2**).

Core	Spacers			Potential energy (kcal/mol)			Difference $\Delta E_{D\text{-}I}$ (kcal/mol)
	S_1	S_2	S_3	Dendrimer E_D	Drug E_I	System 1:1 $E_{D\text{-}I}$	
C-I	TEG	TEG	TEG	−40,713	45,458	13,034	−8,289
	–	TEG	TEG	−87,758	45,458	−28,391	−13,909
	DD	TEG	TEG	15,836	45,458	14,933	46,361
	DD	DD	TEG	96,310	45,458	−74,170	215,938
	–	DD	TEG	−119,993	45,458	−154,060	79,525
C-II	DD	TEG	TEG	62,972	45,458	−5,874	114,304
	DD	DD	TEG	−102,930	45,458	31,401	−88,873
C-III	DD	TEG	TEG	41,882	45,458	51,818	35,522
	DD	DD	TEG	−139,903	45,458	32,752	−127,197

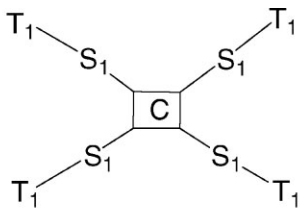
Table 2.
Simulation results for the modeling compounds (**3**)

Core	Molecular dynamic procedure (Yes/No)	Potential energy (kcal/mol)			Difference, ΔE_{D-I} (kcal/mol)
		Model E_D	Itraconazole E_I	System 1:1 E_{D-I}	
C-I	No	71,228	45,458	101,912	14,774
	Yes	19,804	44,315	51,462	12,657
C-II	No	79,367	45,458	107,648	17,177
	Yes	32,636	44,315	51,176	25,775
C-III	No	89,990	45,458	121,233	14,215
	Yes	34,972	44,315	44,807	34,480

and $S_1 = DD$, $S_2 = TEG$ in dendrons showed better energetic effects. However, the $S_1 = 0$, $S_2 = DD$ combination was excluded from subsequent calculations, considering the dendron steric effects at the convergent synthesis of the real compounds.

Next, to evaluate the core influence on itraconazole encapsulation, simulations were made with cores C-II and C-III, and $S_1 = DD$, $S_2 = DD$, and $S_1 = DD$, $S_2 = TEG$ spacer combinations (Table 1), and so the core encapsulation efficiency range could be presented as C-I > C-II > C-III in the case of $S_1 = DD$, $S_2 = DD$, and C-II > C- I> C- III for $S_1 = DD$, $S_2 = TEG$ respectively.

Unfortunately, the use of the whole dendrimer structures (**2**) exceeds the operational capacities of software employed, and so, to perform the molecular dynamic simulations, the less bulky modeling compounds (**3**) having a core, four spacers S1 and succinic terminal groups were proposed. Analogously to calculations for the structures (**2**), simple geometry optimization allowed us to obtain the core encapsulation efficiency range C-II > C- I > C- III (Table 2) similar to that of (**2**) with $S_1 = DD$, $S_2 = DD$.



C - Core: C-I-VI, **S_1 - spacer:** decanediol,
T_1 - terminal group 1: -CO-CH_2-CH_2-COOH

3

However, these results were contrary to those shown with MD: C-III > C-II > C-I (Table 2). We suggest that this could be explained by better conformation-generating possibilities of the method with molecular dynamics procedures, allowing the achievement of ''modeling compound-itraconazole'' (1:1) system organization with more effective electrostatic interactions between itraconazole and core structures. On the other hand, the cores C-II and C-III have more planar and strong architectures, which made it possible to acquire a larger area for itraconazole arrangement. Thus, we think that the results obtained with MD are more certain.

Also, to evaluate the dependence of drug encapsulation by the modeling compounds on dendron quantity, we undertook complementary geometry optimization and molecular dynamic calculations (data not shown) with 3 structures of commercially-available benzene polycarboxylic acid as cores: 1,4-benzenedicarboxylic, 1,3,5-benzenetricarboxylic and 1,2,3,4,5,6-benzenehexacarboxylic acids. The results were less promoting than with the core C-III (1,2,4,5-tetracarboxylic acid) and, thus, theoretically proved tetrafunctional core efficiency.

Conclusion

We have shown that according to the energetic difference values obtained by simple geometry optimization procedures, the more effective itraconazole encapsulating agents are compounds (**2, C-I**) with the decanediol spacer groups S_1 and S_2 in dendrons.

The use of molecular dynamic procedure with model structures (**3**) allowed us to obtain better energetic effects with the core presented by benzene tetracarboxylic acid.

[1] J. Heeres, J.J.L. Backx (to Jannsen Pharmaceutica NV Belg.), EP0006711, **1980.**
[2] S.-Y. Shim, Ji. Ch,-W H. Sah, E.-S. Park, B.-J. Lee, *Arch. Pharm. Res.* **2006**, *29*, 1055–1060.
[3] R. S. Danikula, P. Hildgen, *Bioconjugate Chem.* **2006**, *17*, 29–41.
[4] P. Miklis, T. Çağin, W. A. Goddard, III *J. Am. Chem. Soc.* **1997**, *119*, 7458–7462.
[5] I. Elkin, P. Hildgen, Program and Abstracts of the 13th International IUPAC Conference on Polymers and Organic Chemistry (POC'09), Montréal, Canada, 5- 8 July 2009, Montreal, **2009**, p.129.
[6] D. Rogers, *Computational Chemistry using the PC*, 3rd Edition, John Wiley & Sons, **2003**.
[7] *HyperChemTM 8.0.4 package Molecular Modeling System Software*, Hypercube Inc, Gainesville, FL, USA **2007**.

