



Modified Release Studies on the New Antitubercular Compound (1,1'-[4,4'-[Tricyclo[3.3.1.3.3^{3,7}]]Decane-1,3-Diyl]Bis(Phenoxyethyl)]Dipyrrolidine, Bis-Hydrochloride Salt from Solid Pharmaceutical Formulations.

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Abstract

The modified release of a new, potent antitubercular agent (compound 1), from tablets and hard gelatin capsules, into gastrointestinal-like fluids, was probed. Albeit its high lipophilicity, compared to its congeneric derivative, *SQ109*, the dissolution profile of 1 was found to be in alignment with the release characteristics necessary for antitubercular action (relatively fast initial release followed by a gradient). The excipients used to achieve this dissolution pattern were combinations of sodium alginate, lactose monohydrate, and polyvinylpyrrolidone (PVP).

Keywords: Adamantane derivative, Antitubercular activity, Hydrophilic matrices, Capsules, Modified release.

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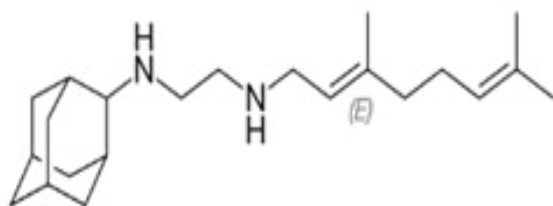
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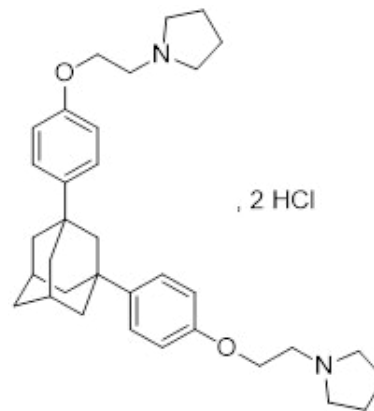
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Introduction

Tuberculosis, an infectious disease usually caused by the bacteria *Mycobacterium tuberculosis* (TB), has been present in humans since ancient times [1]. Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of HIV [2]. Many strains of tuberculosis resist to the drugs mostly used to treat the disease and as a result new drugs and regimens are urgently needed to shorten the required duration of tuberculosis treatment [3]. N-adamantan-2-yl-N²-[(E)-3,7-dimethyl-octa-2,6-dienyl]ethane-1,2-diamine (*SQ109*, Figure 1), is a drug candidate that is active against both drug-susceptible and drug-resistant TB strains and affects cell wall synthesis [4]. Based on these findings, it was recently decided to extend our ongoing research on the chemistry and pharmacology of aminoadamantane analogues [5] by synthesizing and evaluating an analogous derivative of *SQ109*, compound 1 (Figure 1), which showed a noteworthy tuberculocidal activity. Albeit the fact that the lipophilicity of this compound (clogP=9.09) is much higher than that of *SQ109* (clogP=6.82), it is, however, within the allowed limits for oral administration. Therefore, it was intriguing to probe its oral absorption profile, because this information is of paramount importance for future in vivo studies. To this end, we extended, in the context of the present work, our recent studies on the modified release of compound 1, from tablets [6], by encapsulating 1 and the same excipients used in the respective tablets, in hard gelatin capsules.



SQ109: N-adamantan-2-yl-f-[(E)-3,7-dimethylocta-2,6-dienyl]ethane-1,2-diamine



Compound 1: (1,1'-[4,4'-[tricyclo[3.3.1.3.3,7]decane-1,3-diyl]bis(phenoxyethyl)]dipyrrolidine, bis-hydrochloride

Figure 1: Structures of SQ109, and compound 1

Materials & Methods

Matrix tablets and capsules were comprised of compound 1, and combinations of the following excipients: sodium alginate, lactose monohydrate, and polyvinylpyrrolidone (PVP) (Table 1). The dissolution experiments involved flat tablets (10 mm diameter, 200 mg weight and 6-9 Kp hardness) and hard gelatin capsules (No. 0); the release of compound 1, in gastric (pH 1.2 for the first two hours) and intestinal

(pH 6.8 for the following 6 hours) simulated fluids, was determined spectrophotometrically at $\lambda_{\max}=223$ nm (Figures 2a and 2b). The 3D structures of the compounds were produced using the LigPrep 3.4 module and were minimized using the OPLS3 force field (Figure 3). Comparison indices, f_1 and f_2 , were used to compare the dissolution profiles (Table 2).

	F1 (mg)	F2 (mg)	F3 (mg)	CAF1 (mg)	CAF2 (mg)	CAF3 (mg)
Compound 1	5	5	5	5	5	5
Lactose monohydrate	49	-	-	49	-	-
PVP (M.W.: 55.000)	-	63	83	-	63	83
Sodium Alginate	144	130	110	144	130	110
Mg. Stearate	2	2	2	2	2	2
Total	200	200	200	200	200	200

Table 1: Tablet and capsule formulations

	F1-F2	F1-F3	F2-F3	CAF1-CAF2	CAF1-CAF3	CAF2-CAF3
f₁	65.02	76.55	11.84	55.70	48.74	45.17
f₂	13.89	14.71	62.20	21.90	23.86	37.52

Table 2: f_1 and f_2 indices for Formulation 1 – 3

During and after the production of tablets, there were critical checks on their quality. Through these tests, it was found that the properties and characteristics of the tablets meet the necessary standards. Performed tests included weight uniformity, thickness uniformity, hardness and friability measurements and measurement of the tablets. The results obtained were in accordance with the National Pharmacopeia.

Regarding the statistical analysis of the results, and after adjustment of different empirical release models to the experimental data, it was observed that the Peppas-Korsmeyer model was adjusted

satisfactorily in all formulations. The present working data follow a normal distribution; therefore, the statistical processing conforms to the parametric t-test and ANOVA tests.

Results & Discussion

In the case of the tablets, the results obtained suggest that the use of the diluent lactose, instead of polyvinylpyrrolidone (PVP), brings about a more rapid release of the active substance. Moreover, when the relevant weight ratios of sodium alginate and PVP varied, with the amount of the binder PVP increasing, the release of the active substance was retarded (Figure 2a).

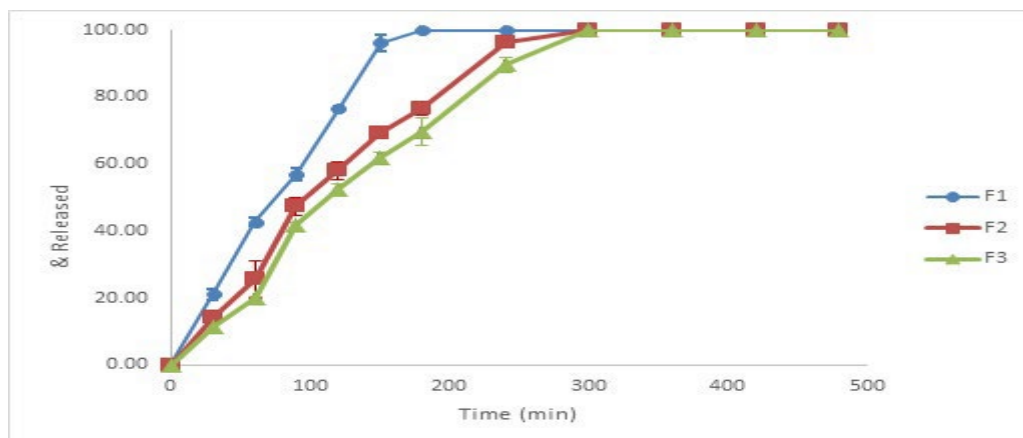


Figure 2a: Drug release of Compound 1 from F1, F2 and F3

This trend was also followed and in the case where the active ingredient and the above excipients were encapsulated in hard gelatin capsules. However, as noticed from the respective dissolution curves

(Figure 2b), compound 1 is released relatively faster from the capsules than from the tablets. This could be attributed to the facile solubilization of the capsules, and therefore to the prompt release of their contents into the gastrointestinal-like fluids.

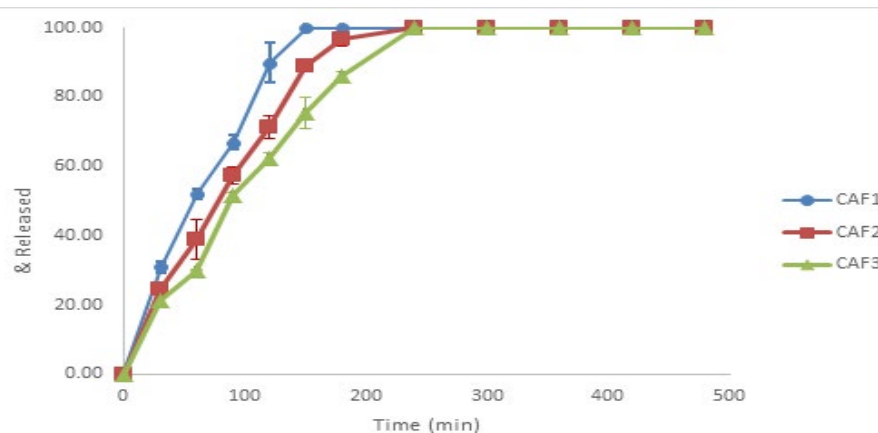


Figure 2b: Drug release of Compound 1 from CAF1, CAF2 and CAF3

The fact that the high lipophilicity of compound 1 does not impede its preferable, for antitubercular action, dissolution, is possibly attributed to the energetically favored conformation it adopts. As shown in Fig-

ure 3, the two aromatic rings are in spatial vicinity. As a result, a large number of water molecules are trapped in between, leading to effective aqueous- π electron interactions via hydrogen bond formation^[7].

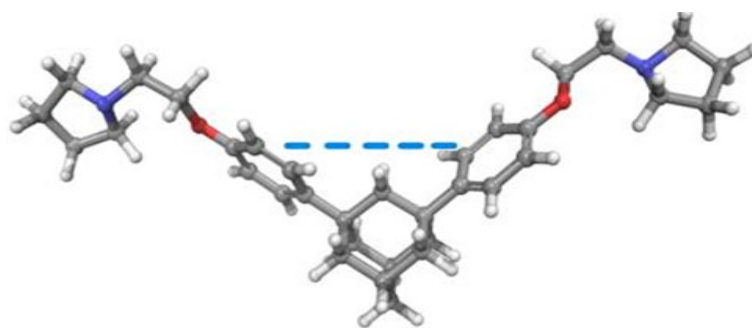


Figure 3: 3D-structure of compound 1, (1,1'-[4,4'-[tricyclo[3.3.1.1.3,7]decane-1,3-diyl]bis(phenoxyethyl)]dipyrrolidine, bis-hydrochloride

Conclusions & future work

A new potent tuberculocidal compound, albeit being lipophilic, showed a satisfactory controlled release profile, comparable to SQ109. Taking into account that there is an urgent need for effective and side effects devoid antitubercular agents, information about the oral absorption profile of compound 1 will be very useful in future in vivo studies.

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