Racemization of Ibutilide in Solution: A Factor to Consider When Choosing to Develop the Racemate or a Single Enantiomer

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INTRODUCTION

Increasing regulatory attention is being paid to the development of racemic drugs. This attention typically centers on the fact that the individual enantiomers often have significantly different pharmacological action, toxicity, absorption, distribution, metabolism, and/or excretion (1). However, physicochemical differences between a racemate and a single enantiomer generally do not receive much attention. Significant differences in properties such as solubility or stability may exist for a racemate and an individual enantiomer (2,3).

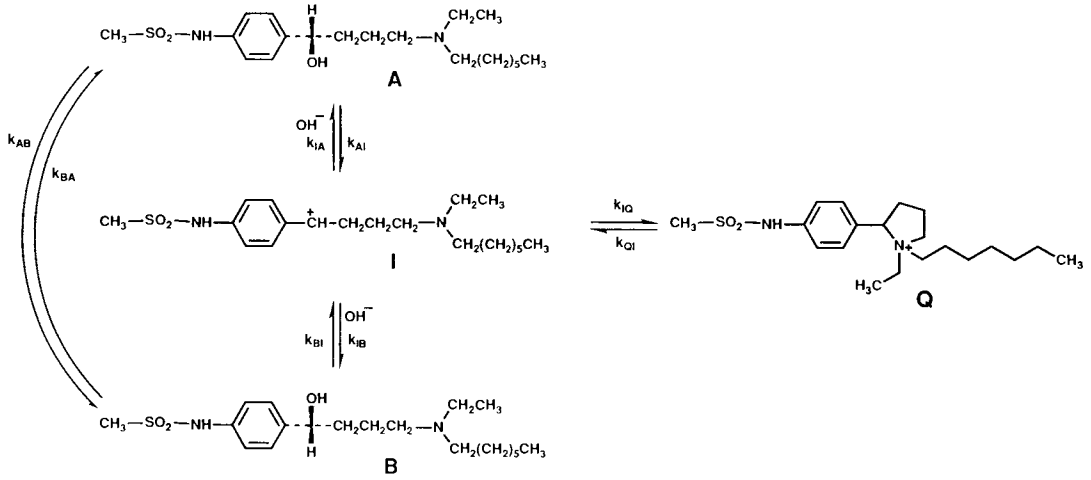
Recently we described the mechanism of racemization of the enantiomers of ibutilide, an investigational Class III antiarrhythmic agent (4). It was shown that racemization proceeds primarily through an S_N2 mechanism, with an S_N1 mechanism accounting for approximately 20% of the racemization at 80°C. Since ibutilide (or its enantiomers) is expected to be useful in the acute treatment of life-threatening arrhythmias, the availability of a sterile solution is desirable from a medical and marketing standpoint. Therefore it was important to determine if racemization proceeds at a rate of room temperature that eliminates the possibility of developing a sterile solution of an enantiomer, since traditional alternatives such as lyophilization or refrigerated storage would hinder acute use. However, the investigation of racemization was complicated by intramolecular nucleophilic attack of the chiral carbon by the tertiary amine of ibutilide (5), a reaction which dominates at elevated temperatures. The present report provides an interesting example of how accelerated stability testing can be utilized with complex reaction mechanisms. In this case, this approach led to the selection of an enantiomer sterile solution formulation with less than 10% degradation in 2 years at 30°C. This report also provides a clear illustration of how ignoring the physicochemical properties of racemic drugs can potentially lead to a pharmaceutically useless drug product.

EXPERIMENTAL

The two enantiomers of ibutilide were prepared by the Chemical Research Preparations Unit of the Upjohn Company and were all greater than 98% pure. Otherwise, reagent-grade chemicals were used throughout the study. Samples were prepared in a pH 4.6 acetate buffer (0.0346 *M*) made isotonic with saline. The drug concentration of all samples was 5.65×10^{-4} *M*, and all samples were duplicated. The concentrations of the two enantiomers and the cyclic quaternary ammonium degradation product were determined by combining data from an achiral potency assay and a chiral assay, both of which have been previously described (4).

RESULTS AND DISCUSSION

Previous evidence suggests that the formation of a cyclic quaternary ammonium degradation product (U-87473) of ibutilide proceeds through a carbocation intermediate (4). Racemization also utilizes this same pathway but is dominated by an S_N2 mechanism (see Scheme I). Evidence for these mechanisms is based on pH–stability data for racemization and quaternary ammonium degradation product



Scheme I. Proposed mechanism for the racemization and cyclization reactions of ibutilide.

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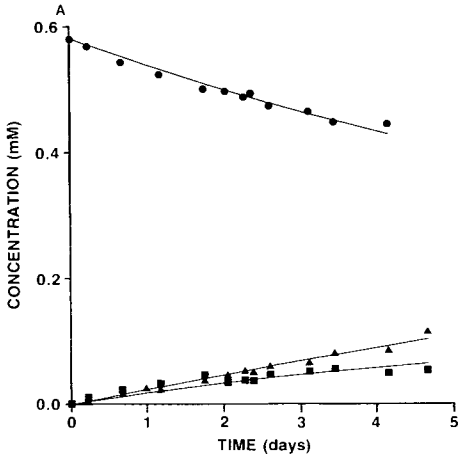

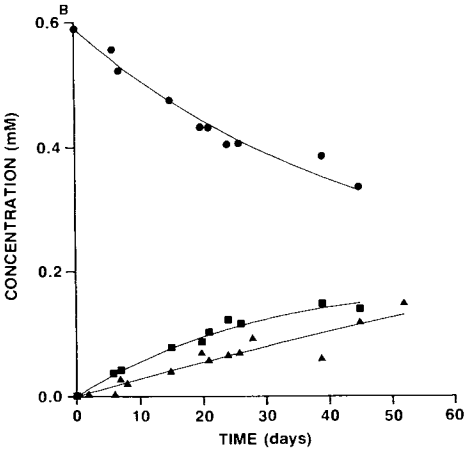

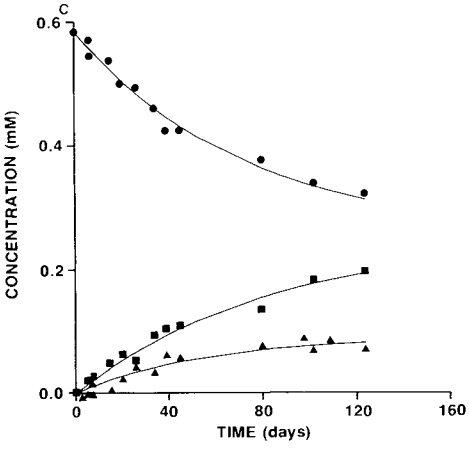

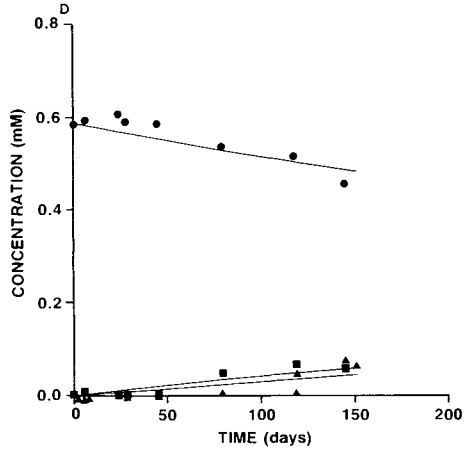

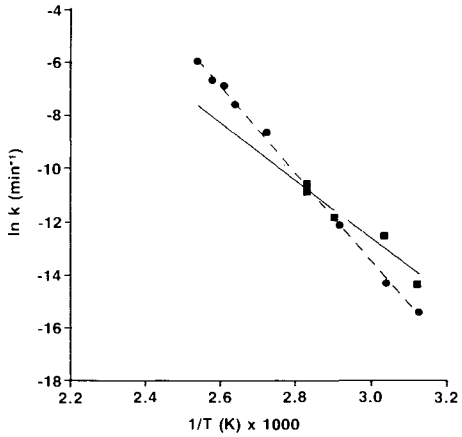

Fig. 2. Arrhenius plots for the loss of ibutilide through quat formation (●) and for k_{AB} (■); see text for definition of rate constants. Data for the quat formation were taken from Ref. 5 (47–121°C).

formation, kinetic analysis, chromatographic evidence that all four stereoisomers of U-87473 form from a single enantiomer, and aniline "trap" experiments which demonstrate that the formation of U-87473 is stopped and that racemization is slowed by a sufficiently high concentration of a good nucleophile. Based on preliminary stability, solubility, microbial challenge, and tissue irritation studies, pH 4.6 was chosen for further study as a prototype formulation.

The primary objective of the present study was to predict the room-temperature shelf life of an enantiomer formulation relative to the racemate. However, traditional Arrhenius analysis of racemization is complicated by the formation of the cyclic quaternary ammonium degradation product. This reaction is very crucial at elevated temperatures due to an unusually high energy of activation (E_a of over 30 kcal/mol) (5). At temperatures of 30°C or less, the cyclization reaction may be ignored. This suggests that the initial rate of racemization at room temperature can be predicted by Eq. (1):

$$k_{rac} = k_{direct} + 0.5\ (k_{inter}) \qquad (1)$$

where k_{direct} and k_{inter} are the extrapolated room-temperature rate constants for the racemization of an enantiomer from the direct S_N2 mechanism and for the formation of the carbocation intermediate by the S_N1 mechanism, respectively (Scheme I). However, such an analysis was found to be impractical due to the large confidence intervals obtained for the rate constants when elevated temperature data were fit by the model in Scheme I (4). It is believed that the poor confidence limits were due to the fact that an excellent fit of the data was also obtained by the same model without the S_N2 mechanism. Thus, the approach used in the present study was to fit the elevated-temperature data to a simple model which ignores the actual details of the reaction mech-

Fig. 1. Concentrations of the original enantiomer (●), the newly formed enantiomer (■), and the cyclic quaternary ammonium product (▲), as a function of time at 80°C (A), 70°C (B), 56°C (C), and 47°C (D). The lines represent the fit of the experimental data to Eqs. (2)–(4).

Table I. Estimated Reaction Rates (Day^{-1})[a]

T (°C)	Enantiomer	$k_{AB} \times 1000$	$k_{AQ} \times 1000$	k_{QA}
80	(+)	34.0 (4.3)	42.0 (7.1)	2×10^{-6} (0.046)
80	(−)	31.2 (5.0)	43.4 (8.1)	1×10^{-6} (0.047)
70	(+)	10.8 (1.2)	4.76 (1.44)	1.0×10^{-5} (0.0074)
70	(−)	9.93 (0.85)	6.17 (0.92)	5.82×10^{-3} (0.0024)
56	(+)	5.01 (0.57)	2.85 (0.86)	7.97×10^{-3} (0.0043)
56	(−)	5.04 (0.89)	2.91 (1.23)	6.34×10^{-3} (0.0058)
47	(+)	0.833 (0.582)	0.533 (0.991)	2×10^{-6} (0.014)
47	(−)	6.16 (5.54)	0.617 (5.64)	1.0×10^{-5} (0.073)

[a] See Eqs. (2)–(4); 95% univariate confidence limits in parentheses.

anism and assumes that the enantiomers and U-87473 are in equilibrium with each other [Eqs. (2)–(4)].

$$dA/dt = k_{BA}(B) + k_{QA}(Q) - (A)(k_{AB} + k_{AQ}) \quad (2)$$

$$dB/dt = k_{AB}(A) + k_{QB}(Q) - (B)(k_{BA} + k_{BQ}) \quad (3)$$

$$dQ/dt = k_{AQ}(A) + k_{BQ}(B) - (Q)(k_{QA} + k_{QB}) \quad (4)$$

In the above equations A, B, and Q signify the concentration of the original enantiomer, the newly formed enantiomer, and the quaternary ammonium product. The rate constants k_{XY} signify the rate of constant for the formation of Y from X. It was also assumed that $k_{AB} = k_{BA}$, $k_{AQ} = k_{BQ}$, and $k_{QA} = k_{QB}$.

Nonlinear regression analysis (PCNONLIN 3.0, SCI Software, Lexington, KY) of simultaneous racemization and "cyclic quat" formation was performed on enantiomer samples at 47, 56, 70, and 80°C (see Fig. 1). Estimated rate constants are given in Table I. In general, there is good agreement for the rates of the two enantiomers. The confidence limits for k_{AB} and k_{AQ} appear to be good, with the possible exception of the 47°C data, where less than 15% of the quat and the new enantiomer were formed over 5 months. Larger confidence limits were observed for k_{QA}, which is likely a result of the relatively low concentration of the quat which formed.

An Arrhenius plot of the rate constant k_{AB} is shown in Fig. 2 along with previous data describing the formation of the quat degradation product (5). The formation of the quat takes place with an unusually high energy of activation (approximately 32 kcal/mol). This high energy may represent the barrier that must be overcome for nucleophilic attack by a tertiary amine. The formation of the carbocation intermediate requires a much lower energy of activation (21.3 kcal/mol; 95% confidence interval of 7.2 kcal/mol). The 47°C data for the levorotatory enantiomer was not included in this analysis due to the high confidence intervals for k_{AB} and k_{AQ}.

Based on an E_a of 21.3 kcal/mol and a preexponential term of 4.81×10^{11} day^{-1}, it can be estimated that k_{AB} at 30 and 25°C would be 1.99×10^{-4} and 1.16×10^{-4} day^{-1}, respectively. These rates correspond to a time for 10% loss of an enantiomer of approximately 1.5 and 2.5 years, respectively. While these estimates are considered rough due to the use of a simplified degradation model, the results suggested that it was worthwhile to generate real-time data for racemization.

Data at 30°C are currently available for both enantiomers through 6 months (see Fig. 3). Initial rate analysis suggests that the dextrorotatory and levorotatory enantiomers racemize at a rate of 0.345% (0.024) and 0.317% (0.013) per month, respectively (95% CI in parentheses). This represents a time for 10% loss of approximately 2.5 years at 30°C. Thus, the proposed enantiomer formulation has a pharmaceutically acceptable shelf life. However, had the rate of racemization been 10-fold faster, the feasibility of producing a sterile solution with an acceptable shelf life would have been poor for an individual enantiomer. Either freeze-drying or subambient storage would have been required, both of which are considered inferior options from a medical or marketing standpoint. Alternatively, if the pharmacokinetic or pharmacodynamic differences between the two enantiomers are insignificant, it may be desirable to develop the racemate instead of a single enantiomer (racemization cannot be observed with a racemate and is, therefore, not a stability issue). Thus, it is possible that the solution state stability of the racemate versus the individual enantiomers may play a key role in the decision of which compound to develop.

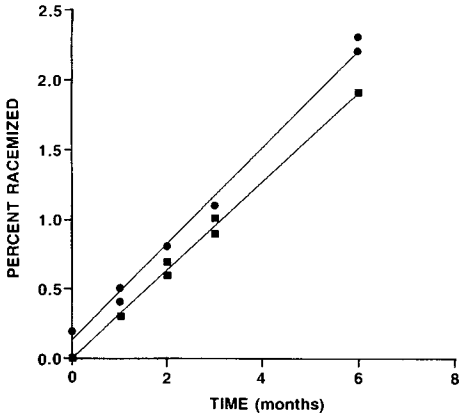

Fig. 3. Percentage of newly formed enantiomer in solutions of the dextrorotatory enantiomer (●) and the levorotatory enantiomer (■) of ibutilide at 30°C.

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