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NOTE

NEW REALISTIC APPROACH OF THE KINETICS IN FAST LABELLING PROCEDURES.

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Summary

A real kinetic approach of fast labelling reactions is obtained by introducing a corrected reaction time τ which takes into account the temperature rise process of the reaction solution. τ is obtained by transformation of transient temperature data to isothermal conditions at a preset temperature.Experimental data obtained for ^{123}I-radioiodination of ortho-iodohippuric acid fit completely with the theory.

Key-words: accurate kinetics, fast labelling, temperature-time conversion, corrected reaction time.

Introduction

Fast kit preparations are more and more propagated as being the future of radiopharmaceuticals labelled with short-lived isotopes such as ^{123}I (1,2). As the major requirement is to yield a pure radiopharmaceutical the study of the kinetics during its develop-

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ment is a real must. The study of the kinetics in kit-labelling conditions is not well described until now. The theory and technique proposed in this paper allows the realistic and accurate approach of the kinetics involved with fast labelling by taken into account the heating up period required to bring the reaction mixture to the preset temperature. The fast labelling of ortho-iodo hippuric acid (Hippuran) with ^{123}I is shown as a case study.

Theory

For fast labelling reactions a considerable part of the reaction can occur during the heating up period required to bring the reaction mixture from room temperature to the preset reaction temperature. This means that the reaction rate constant continuously changes during this heating up process until equilibrium temperature (T_{eq}) is reached. To obtain a realistic approximation of the kinetics and accounting for the temperature rise process a corrected reaction time τ is introduced. τ is defined as the time necessary to obtain at a constant reference temperature T_{eq} a conversion equal to the conversion obtained at transient time t of the heating up period (T_t :temperature at t). This means in practice a transformation of the time data under transient temperature conditions to time data under isothermal conditions at the preset equilibrium temperature.

Mathematically τ can be expressed by :

$$\tau = \int_0^t \frac{e^{-E/RT}}{e^{-E/RT}} dt$$

E : activation energy estimated from literature, experiments at equilibrium temperature or through an iterating convergent algorithm.

Results and Discussion

The principle is demonstrated by the application of the theory on the fast kit labelling of ortho-iodo hippuric acid with $^{123}I^-$ by nucleophilic exchange in reducing acidic medium at 70°C (see experimental). An activation energy E of 11050 cal was calculated from an Arrhenius plot obtained by carrying out labelling experiments in preheated conditions at 40, 50, 60 and 70°C (the sample is heated up to equilibrium temperature before adding the $^{123}I^-$). The figures 1 a and 1 b respectively show the temperature rise curve and the labelling yield η in % (activity of ^{123}I-Hippuran/total activity of ^{123}I x 100) as a function of time when applying kit-labelling conditions. These curves demonstrate that at least half the reaction occurs before reaching the equilibrium temperature. The sigmoid curve (1 b) is typical for kinetic results obtained for reaction systems which are not at temperature equilibrium and thus showing a lag period.

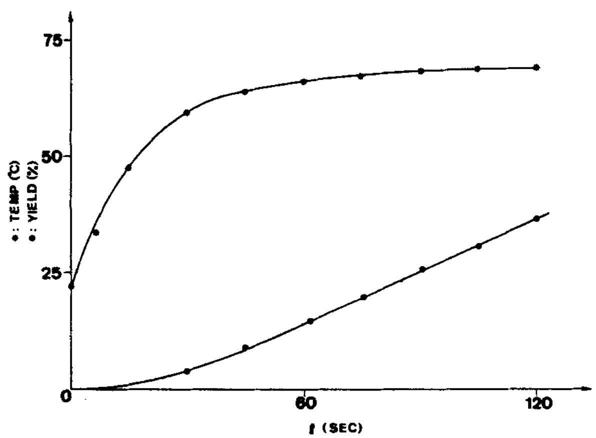

Fig.1 *:Temperature rise curve measured in the reaction solution
•:Labelling yield η as a function of time when applying kit labelling conditions

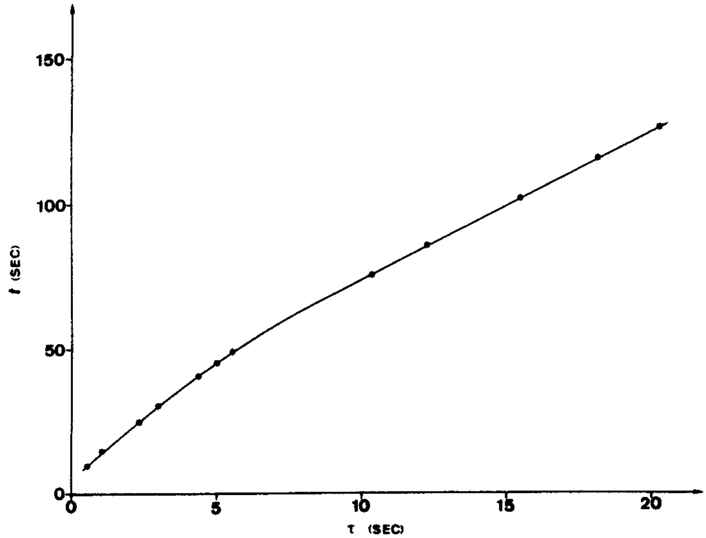

Fig.2 t,τ relationship for the estimation of the corrected time.

Figure 2 shows the t, τ relationship allowing the estimation of the corrected time τ . τ is calculated applying equation 1 and introducing the E value of 11050 cal. mentioned above.

Figure 3 shows that the labelling yields η (in %) obtained under transient temperature conditions but plotted as a function of the corrected time applying the τ theory, coincide with the curve obtained in temperature equilibrium conditions (preheated conditions).

This proves that the theory is valid for the the part of the η , t curve which is of interest in kinetic studies.

This theoretical approach opens new pathways for a real kinetic study when applying fast labelling conditions.

Experimental

Labelling conditions - 1 mg of custom purified O-I-hippuric acid (HPLC controlled purity > 99,9 %), 5 mg of ascorbic acid, 15 µl of a $CuSO_4$ solution (32.5 mg $CuSO_4.5H_2O$/10 ml H_2O), 1 ml of H_2O

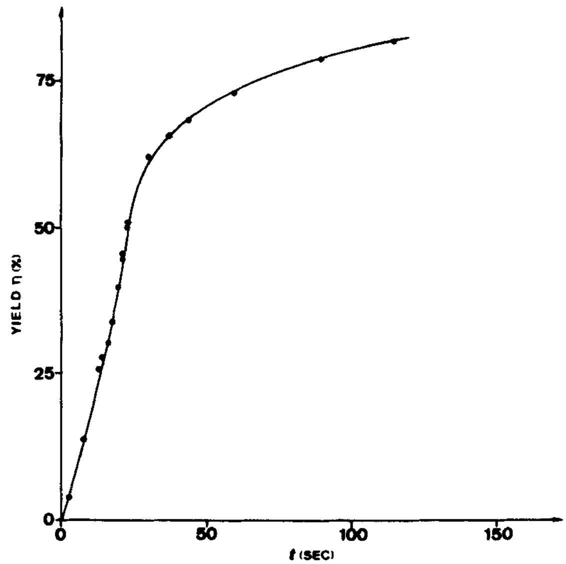

Fig.3 •:Labelling yield in temperature equilibrium conditions (preheated conditions)
*:Labelling yield under transient temperature conditions but with time correction.

and 1-2 mCi of $^{123}I^{-}$ solution (act. conc. 0.4 mCi/µl) are heated at 70°C in a septum closed penicillin vial.

Kinetic data - are obtained by sampling of small aliquots which are immediately quenched in pre-cooled minivials containing a large excess of HPLC eluent.

Radio-HPLC conditions - The HPLC system consists of a Waters set-up (U6K injector, M 6000 pump, Lambda Max 480 UV detector) coupled to a γ scintillation detector unit (3"NaI(Tl) Ortec, Ortec electronics) and Shimadzu R3A integrators.Chromatography is carried out on a Chrompack Lichrosorb 10 RP18, 250 x 4.6 mm column using a mixture of H_2O/Methanol/Acetic acid - 70/29.5/0.5 as eluent.

Temperature-time curves - a low mass and fast response thermo couple (NiCr-Ni 0.5mm Ø ,Heju Tastotherm 700) is introduced through the septum into the reaction vial which, containing the appropriate volume of reaction solution, is submitted to the prescribed reaction conditions. The temperature rise curve is measured by means of a custom made amplifying system and appropriate x, t recorder (BD 40 Kipp-Zonen).

Acknowledgement

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