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PURPOSE. *Threo*-Methylphenidate undergoes base catalyzed enolization to form *erythro* isomer in the MethyPatch[®] transdermal system (TDS). This degradation pathway is highly sensitive to the storage temperature. The current ICH guideline uses 6-month 40°C/75% RH (relative humidity) as accelerated condition, or 12-month 30°C/60%RH as intermediate storage condition to establish 2 year RT (25°C/60%) shelf life. The purpose of this report is to provide support and rationale for proposing 3-month 40°C/75%RH as the accelerated model to accurately predict the extent of degradation through 24-month RT storage for MethyPatch[®].

METHOD. The stability profile was characterized under 40°C/75% RH, 30°C/60% RH, and 25°C/60% RH. The content of *erythro* isomer in MethyPatch[®] over time was analyzed with HPLC. The HPLC conditions were:

Column: C18 (0.46cm × 15cm, 5µm).
Mobile Phase: Buffer (25mM KH₂PO₄, 8 mM C₈H₁₇SO₃Na, pH was adjusted to 2.6± 0.1 with H₃PO₄) : Acetonitrile (75:25, v/v).
Flow Rate: 1.2 mL/min.
Detection: UV at 210 nm wavelength.

RESULTS. a: % *erythro* Isomer vs. Time
The degradation reaction of *threo*-methylphenidate to *erythro* isomer follows first order kinetics model at all studied conditions (see fig. 1).
(with 1st order kinetics: $\ln(1-x) = -kt$, x : % *Erythro* isomer, when $x \ll 1$, $x = kt$)

Table1: % *Erythro* Isomer* Under Different Temperature vs. Time

Month	25°C/60% RH	30°C/60% RH	40°C/75% RH
0	0.2	0.2	0.2
1	0.3	NA	0.8
2	0.4	NA	1.5
3	0.6	NA	2.2
6	0.6	1.2	4.0
9	0.8	1.5	NA
12	1.0 *	2.1 **	NA

* All data are the average of 27 ICH lots, except: * average of 16 ICH lots, **average of 12 ICH lots.

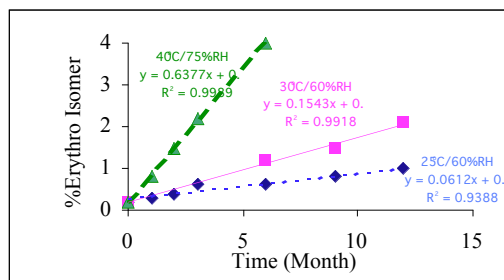


Fig. 1 *Threo*-Methylphenidate to *Erythro* Isomer Reaction Rate

b: Degradation Rate Constants vs. Temperature

The logarithm of reaction constant versus the reciprocal of temperature in Kelvin follows the trend predicted by Arrhenius equation (see Fig. 2) with activation energy of 114 kJ/mol (13677/8.314 J/mol).

Table 2: Rate Constant vs. Temperature

T (K)	k	1/T	Ln k
298	0.0612	0.00336	-2.7936
303	0.1543	0.00330	-1.8689
313	0.6377	0.00319	-0.44989

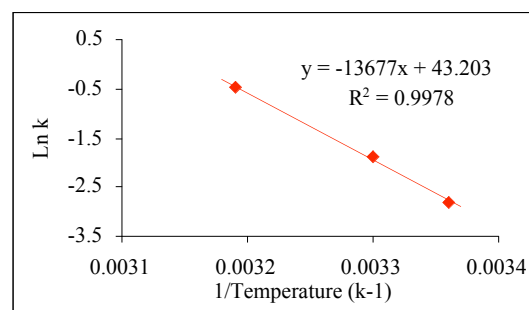


Fig. 2 Arrhenius Equation of *threo*-Methylphenidate to *erythro* Isomer Reaction Rate vs. Temperature

CONCLUSIONS.

- The reaction of *threo*-Methylphenidate base to *erythro* isomer in MethyPatch[®] TDS Vs. time follows apparent 1st order kinetics model, with an excellent agreement between the stability data and the projection trend. This kinetics model suggests 1.7% *erythro* isomer after 24-month RT (25°C/60% RH) storage.
- The reaction of *threo*-Methylphenidate to *erythro* isomer follows the same mechanism under the three ICH conditions (40°C/75%RH, 30°C/60%RH, and 25°C/60%RH), therefore, the reaction rate can be accurately predicted at any given temperature within the range of 25°C – 40°C using Arrhenius equation.
- Due to the relatively high activation energy ($E_a=114$ kJ/mol) required for this degradation pathway, *threo*-Methylphenidate to *erythro* isomer in MethyPatch[®] is highly temperature dependent. The conventional accelerated conditions (6-month 40°C/75%RH) and the intermediate storage condition (12-month 30°C/60%RH) over-estimated this degradation.
- Quantitatively, 2.3 month 40°C/75% RH or 9.5 month 30°C/60%RH storage is equivalent to 24-month 25°C/60%RH for monitoring the content of *erythro* isomer in MethyPatch[®]. Based on this kinetic study, we propose 3-month 40°C/75%RH as the accelerated model to evaluate the finished product's stability through its shelf life.