META-ANALYTIC APPROACH TO EVALUATE ALTERNATIVE MODELS FOR CHARACTERIZING THE PK PROFILES OF EXTENDED RELEASE FORMULATIONS OF MPH

R. Gomeni[1], F. Bressolle[1], T. J. Spencer[2], S. V. Faraone[3]

[1]*Pharmacometrica, Longcol, La Fouillade, France*

[2]*Massachusetts General Hospital, Boston, MA,* [3]*SUNY Upstate Medical University, Syracuse, NY*

Background

Methylphenidate is a central nervous system stimulant used to treat children over 6 years old, adolescents, and adults with attention-deficit hyperactivity disorder (ADHD). Methylphenidate immediate release formulations should be given one to three times a day to provide symptom coverage throughout the day. Several extended-release formulations usually characterized by a dual release process have been developed for improving efficacy.

Objective

The aim of this work was to propose a novel methodology to evaluate the most efficient PK model to characterize the complex PK profile of MPH, to link in-vivo release with in-vitro dissolution data and to assist development of optimized MPH formulations.

Methods

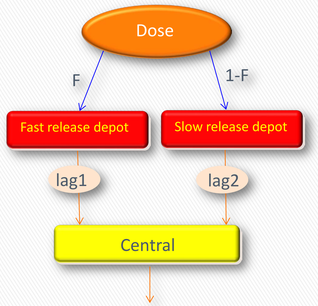
Data extracted from 9 publications describing the MPH PK following the administration of Concerta ® (16mg, 36mg, and 54mg) were used for model development.

The validation of the performance of the best performing model was conducted by fitting the PK profiles of different commercial formulations of MPH: Aptensio XR®, Metadate ER®, Quillivant XR®, Ritalin LA®, Focalin XR®.

Three models were evaluated :

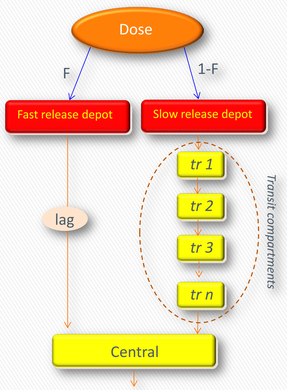
Model 1

Two parallel inputs: The drug absorption rate from the GI tract is defined by a dual first order process with different lag times (lag1 & lag2)



Model 2

Two parallel inputs: one with a lag time and one with a delayed release modeled using a transit compartment (tr) approach.



Model 3

The basic assumption is that we know the structural model describing the input function (f(t)). Then, assuming linear and time invariant disposition with respect to the input, the MPH plasma concentration (C_p), resulting from an arbitrary dose, can be described by convolution as:

$$C_p(t) = f(t)*d(t) = \int_0^t f(t)\cdot d(t-\tau)\cdot d\tau$$

where f(t) is the rate of *in-vivo* drug delivery, * is the convolution operator, and d(t) is the unit impulse response. In case of a simple disposition process (say one compartment), the model equation describing $C_p(t)$ can be written as:

$$\frac{dC_p}{dt} = f(t) - K\cdot C_p \qquad where \quad f(t) = \frac{dr}{dt}$$

Assuming that the fraction of the dose released can be described by the function r(t) (input function), we can solve the previous equation by estimating f(t) as the first derivative of r(t). This can be computed analytically or can be approximated using the finite differences approach.

Implementing the convolution-based model in NONMEM

Assuming a one compartment linear model with a Weibull in-vivo drug release r(t). The convolution-based model using the finite difference approximation can be implemented in NONMEM as:

$$r(t) = e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)}$$

```
DELT=0.001
.......
$DES
        TT1=T-DELT
        TT2=T+DELT
        IF(TT1.LE.0 )TT1=0
        IF(TT2.LE.0) TT2=0
        ABS1=EXP(-(TT1/TD)**SS
        ABS2=EXP(-(TT2/TD)**SS
        Ft=(ABS1-ABS2)/(TT2-TT1)
        DADT(1)=-A(1)*Ft
        DADT(2)=A(1)*Ft-KEL*A(2)
```

The multi-phase release profile of MPH products in-vivo and in-vitro were modeled using a double Weibull function r(t):

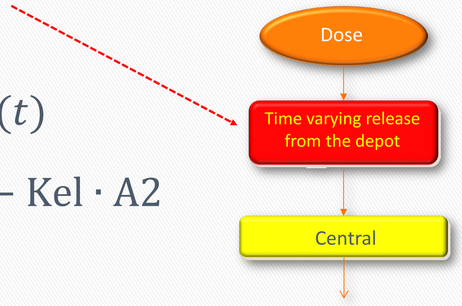
$$r(t) = ff\cdot e^{-\left(\left(\frac{time}{td}\right)^{ss}\right)} + (1-ff)\cdot e^{-\left(\left(\frac{time}{td1}\right)^{ss1}\right)}$$

ff = fraction of the dose released in the 1st process
td = time to absorb 63.2% of the dose released in the 1st process
td1= time to absorb 63.2% of the dose released in the 2nd process
ss= sigmoidicy factor for the 1st process
ss1= sigmoidicity factor for the 2nd process

$$f(t) = \frac{dr}{dt}$$

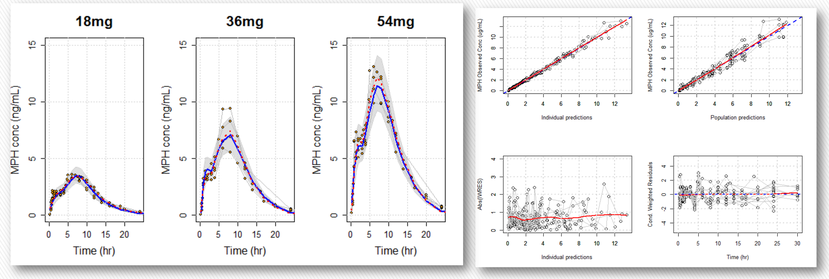
$$\frac{dA1}{dt} = -A1 * f(t)$$

$$\frac{dA2}{dt} = A1 * f(t) - Kel\cdot A2$$



Results

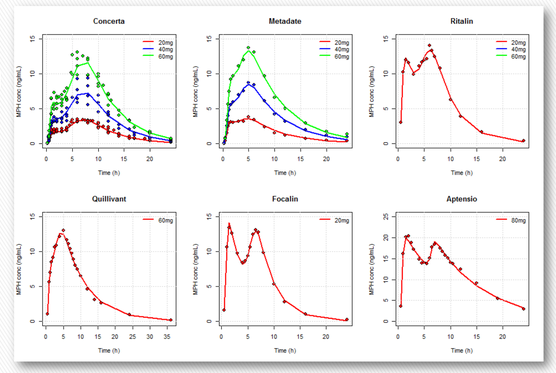
The comparison of the three models performances (goodness of fit, residual plots and AIC criteria) indicated that the convolution-based approach performed better than the models 1 and 2.



Concerta® PK model results: Observed (dots) and model predicted (blue line) MPH concentration (left panel) with goodness-of-fit plots (right panel)

A validation of the performance of the convolution-based model was conducted by fitting the PK profiles of MPH released by different release mechanisms for

- Aptensio XR®,
- Metadate ER®,
- Quillivant XR®,
- Ritalin LA®,
- Focalin XR®.



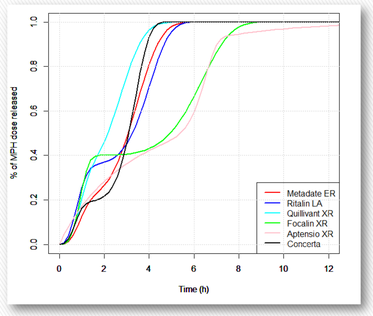
Observed and model predicted MPH profiles for the different formulations

Compare the in-vivo MPH release rate of the different formulations to Concerta®

The same methodology adopted by regulatory agencies for assessing the similarity between 2 dissolution profiles.

- **f1 criterion** (difference factor): calculates the %difference between the test and reference curves
- **f2 criterion** (similarity factor): measure the similarity in the % absorption between the test and reference curves

Generally, f1 values up to 15 (0-15) and f2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves.



In-vivo release rate of the different MPH formulations

		f1	f2
Metadate	ER	4.6	66.4
Ritalin	LA	10.5	49.8
Quillivant	XR	11.8	43.3
Focalin	XR	34.3	27.2
Aptensio	XR	33.3	26.3

Conclusions: The convolution-based model provided a better description of the complex PK profiles of a large variety of extended release MPH products. Among the MPH formulations evaluated, Metadate ER satisfy both the f1 & f2 criteria indicating a small difference (<10) and high similarity (>66) with the in-vivo release of Concerta®