SHORT COMMUNICATIONS

Mathcad: A Tool for Designing Sustained Release Formulations

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Although sustained release drug delivery systems were introduced in the market at the begining of 1960's it became popular only after 1970. In order to maintain blood levels of a drug within the safe margin, calculated doses of the drug need to be given at different time intervals or one preprogrammed drug delivery system need to be given which will release drug at a rate and for a period as per the therapeutic need.[1] *Fig.1* represents plasma drug levels versus time curve for a drug administered as conventional dosage form, (I), and sustained release dosage form (II)[2].

THE most useful method for the examination of drug release in the human body has been through the use of mathematical models, before carrying out experiments. Data analysis, iterative calculations and manual graph plotting are difficult parts of the mathematical models. Software programs like MATHCAD can be used to work with mathematical models. MATHCAD can handle derivatives, integrals, statistical operations, iterative calculations and graphs on log or linear axis.[3] MATHCAD is very user friendly and requires minimal knowledge of computers as per se for its use.

In a sustained release formulation, fraction of the dose (D_i, loading dose) is released immediately and the remaining (D_m, Maintenance dose) is released in a controlled way[4].

Total dose = $D_i + D_m$

Loading dose can be calculated using the expression:

$$D_i = D_m - R_o.t$$

and maintenance dose can be calculated using the expression:

$$D_m = R_o.t$$

where R_o is the rate of release of drug from the maintenance part and t is the period over which the drug is released from the formulation.

To estimate the design parameters for optimized first order release model, MATHCAD can be used. The data and equations can be placed and calculations can be done just as one would do on paper using standard mathematical symbols, unlike other softwares which need a formatted program.

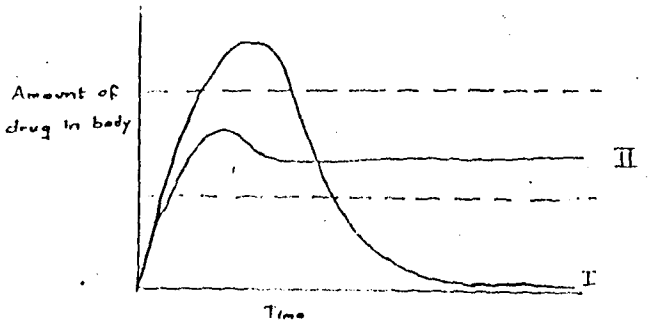

Fig. 1: Hypothetical drug level-time curves of a drug in different dosage forms.

*For Correspondence.

$h := 9.2 \qquad Tp := 1.2 \qquad ka := 2.0$

$Cp := 0.75 \qquad Vd := 1 \qquad f := 0.75 \qquad F := 1$

$$Tm := \frac{4.6}{ka} \qquad Tm = 2.3$$

$$Ti := \frac{h - Tp}{2} \qquad Ti = 4$$

$$Di := Vd \cdot \frac{Cp}{f} \cdot \frac{1}{F} \qquad Di = 1$$

FIGURE 2: This figure denotes the basic values which are provided to a Formulation Chemist to design a sustain release formulation.

$Tp := 1.2 \qquad kr_1 := 0.27 \qquad ka := 2.0 \qquad ke := 0.23 \qquad Am := 0.74$

$Cp := 0.75 \qquad Vd := 1 \qquad f := 0.75 \qquad F := 1$

$$Tm := \frac{4.6}{ka} \qquad Tm = 2.3$$

$$Ti := 2.3 \cdot \frac{\log\left[\frac{kr_1}{ke}\right]}{kr_1 - ke} \qquad Ti = 4.004$$

$$Di := Vd \cdot \frac{Cp}{f} \cdot \frac{1}{F} \qquad Di = 1$$

$$Ai := Di \cdot \frac{ka}{ka - ke} \cdot \exp(-ke \cdot (Ti + Tm)) \qquad Ai = 0.265$$

$$Dm := ke \cdot \frac{Am - Ai}{kr_1} \cdot \exp\left[kr_1 \cdot (2 \cdot Ti - Tm)\right] \qquad Dm = 1.889$$

FIGURE 3:Release kinetics to match the required profile for the duration after administration in which the drug is effectively absorbed.

$h := 9.2 \quad Tp := 1.2 \quad kr_1 := 0.27 \quad ka := 2.0 \quad ke := 0.23 \quad Am := 0.74$

$Cp := 0.75 \quad Vd := 1 \quad f := 0.75 \quad F := 1$

$$Tm := \frac{4.6}{ka} \qquad Tm = 2.3$$

$$Ti := \frac{h - Tp}{2} \qquad Ti = 4$$

$$Ti := 2.3 \cdot \frac{\log\left[\frac{kr_1}{ke}\right]}{kr_1 - ke} \qquad Ti = 4.004$$

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$$Dm := ke \cdot \frac{Am - Ai}{kr_1} \cdot \exp\left[kr_1 \cdot (2 \cdot Ti - Tm)\right] \qquad Dm = 1.889$$

FIGURE 4: Parameters for an ideal sustained release preparation i.e total time after administration in which the drug is effectively absorbed and the release rate constant of the maintenance dose.

T_p = Peak Time
Kr_1 = Firstorder rate constant
A_m = Maximum body drug content to be maintained
A_i = Amount of drug required as maintenance dose
F = Bioavailability factor
f = Fraction of Dose D_i at peak
h = Total time after administration in which the drug is effectively absorbed
K_a = Absorption rate constant
K_e = Elimination rate constant
T_m = Time at which release of maintenance dose begins
T_i = Time at which the blood level profiles of loading and maintainance dosing intersect.
C_p = Peak plasma concentration
V_d = Volume of distribution.

Once k_e of the drug is determined, the release rate of the drug, kr_1, from the sustained release dosage from can be calculated, an easier program for interative calculation of kr_1 is attached along with.

A program for interative calculation of kr1 in BASIC language:

```
10 KR1 = : KE=0.23

20 A = LOG (KR1 / KE)/(KR1 - KE)
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```
30 IF A >= 4 THEN 60 ELSE 40

40 KR1 = KR1 - 0.01

50 GOTO 20

60 PRINT KR1

70 END
```

Thus from **fig 2.** one can calculate the loading dose, the total duration over which the formulation is to spurt the drug in the body, and the time at which release of maintenance begins. **Fig. 3** will help the formulation designer to calculate release kinetic profile and maintenance dose.

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Extractive Spectrophotometric Determination of Antihistaminic Drugs

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A sensitive spectrophotometric method has been developed for determining orphenadrine and diphenyldramine hydrochlorides from its pharmaceutical formulation based on solvent extraction into chloroform of the complexes formed with bromocresol green, bromophenol blue and methyl orange. Complex formation and extraction was complete and quantitative at pH 4. Direct determinations in capsule and tablet preparations were carried out satisfactorily and the average recovery was 100±1.0%.

ORPHENADRINE hydrochloride (ORH) and diphenhydramine hydrochloride (DPH) are antihistaminic agents. Orphenadrine hydrochloride is frequently used in the therapy of parkinsons disease and drug-induced parkinsonism. It has been in use for many years and studies of its metabolic fate in the rat, monkey and man have reported.[1] Spectrophotometric.[2,3] and chromatographic[4,5] methods have been proposed for the determination of ORH. However, these methods are complicated and not sensitive enough. Diphenhydramine, an antihistamine drug that is used in various formulations is analysed by method such as nonaqueous titration[6], potentiometric titration[7], ion-exchange separation[8], quantitative thin layer chromatography,[9] fluorimetric[10] and other routine techniques. However these methods lack the simplicity and sensitivity for routine analysis of pharmaceutical preparations. Spectrphotometric methods have also been used for the analysis of the base. Ion-pair formation with