Pharmacokinetics & Pharmacodynamics of Controlled Release Systems

Presented By: Govardhan.P

Dept. of pharmaceutics,
University College of Pharmaceutical Sciences,
Kakatiya University, Warangal-506009.

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Controlled release:

The term controlled release is associated with therapeutic agents that may be automatically delivered at predetermined rates over long period of time.

The main Goals are :

- To reduce the frequency of dosing
- To increase the effectiveness of the drug by localizing it
- To reduce the dose required
- To provide uniform drug delivery

PHARMACOKINETIC MODELS FOR CONTROLLED DRUG DELIVERY

Several models have been proposed to explain the pharmacokinetic behavior of controlled drug delivery systems.

- Models of time course profile of absorption and elimination
- Loo-Riegelman and Wagner-Nelson model
- Model independent pharmacokinetic analysis

MODELS OF TIME COURSE PROFILE OF ABSORPTION AND ELIMINATION

- Based upon either zero order or first order rate constants for absorption and elimination.

- ✓ Zero order absorption followed by first order elimination.
- ✓ Slow first order absorption followed by first order elimination.
- ✓ Rapid first order absorption of part of those, then release and absorption of the reminder dose over an extended period of time by zero order kinetic process followed by first order elimination process.
- ✓ Rapid first order absorption of part of those ,then release and absorption of the reminder dose over an extended period of time by slow first order kinetic process followed by first order elimination process.

ASSUMPTIONS:

- The elimination of the drug follows first order process
- The rate of distribution is governed by the rate of drug absorption (drug elimination when $k_a < k_e$)
- All kinetic process, except for drug absorption, are linear.

ZERO ORDER ABSORPTION FOLLOWED BY FIRST ORDER ELIMINATION

$$C = \frac{Fk_0}{V k_e}(1 - e^{-KeT})$$

k_O = zero order drug release, rate constant (=absorption)

This equation is similar to constant rate i.v. infusion

Limitations:

- ✓ Time to reach steady state (95%) conc. requires 4.3 half lives
- ✓ For oral release, SS is not possible for a drug with $t_{1/2}$= 3 hr, because the mean residence time is 12 hours in the GIT.

First Order Absorption Followed by First Order Elimination

- The concentration of the drug after single dose administration from sustained release product following first order release kinetics can be given by,

$$C_1 = \frac{FDk_a}{V(k_a - ke)} (e^{-ket} - e^{-kat})$$

- Repeated dosing of first order release formulation generally observes, lower C_{max} and higher C_{min} and longer T_{MAX} in comparison to conventional release formulation
- When $k_a < k_e$ flip-flop phenomenon is observed.

Rapid first order absorption of part of those, then release and absorption of the reminder dose over an extended period of time by zero order kinetic process followed by first order elimination process

❖**The release of the drug from dosage forms occur in two ways :**

First a fraction of the total dose is released for immediate availability to be absorbed by first order process and the remaining fraction is absorbed at constant rate i.e ., a slow zero order process which results in zero order absorption over a prolonged period time

$$C = \frac{FD_l k_0}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) + \frac{Fk_0}{Vk_e}(e^{-k_e t})$$

- With this model, both the rate of decline of drug levels from the fast release component and the rate increase in level due to slow zero order release component are controlled by drug elimination rate constant.

Rapid first order absorption of part of those ,then release and absorption of the reminder dose over an extended period of time by slow first order kinetic process followed by first order elimination process

❖ The amount of drug after single dose administration from a sustained release product equipped with fast release(1st release) component followed by a 1st order release kinetics.

$$C = \frac{FDk_a}{V_1(k_a - k_{10})}(e^{-k10t} - e^{-kat}) + \frac{FD_M k_r}{V_1(k_r - k_{10})}(e^{-k10t} - e^{-krt})$$

Models of time course profile of absorption and elimination

Limitations:

- It may be difficult to one of the four models per fitting analyzing experimental data at obtained after oral administration of sustained release dosage form.
- The absorption rate for sustained release products may be slower the after conventional dosage form ,it may be mixed or combined first and zero order process therefore can not be precisely described by a single model – dependent equation

Loo-Riegelman Model

- Loo-Riegelman model assesses drug absorption in general and specifically absorption from sustained release delivery systems and to determine pharmacokinetic order of the absorption process.
- This model states that the amount of drug absorbed at any given time is equal the sum of the amount of drug present in central comportment and peripheral comportment and of the amount eliminated by all routes.
- The only assumption with this model is the drug pharmacokinetic can be described by at least two compartment model.
- To use this model a drug must be given by the i.v. route as reference.

$$(X_A)_T / (X_A)_\infty = C_T + k_e \int_0^T C dt + (X_P)_T / V_C / k_e \int_\infty^\infty C dt$$

- Two approximations can be made from kinetic equation using Loo-Riegelman model:

- ✓ If a plot of percent unabsorbed [100(1-$(X_A)(X_A)_\infty$] versus time on semi logarithmic plot yields a straight line, it is suggestive of a apparent 1st order absorption kinetics.

- ✓ If a plot of percent unabsorbed [100(1-$(X_A)(X_A)_\infty$] versus time on a rectilinear plot yield a straight line, it is suggestive of an apparent zero order absorption kinetics.

Wagner-Nelson method

- ✓ Wagner-Nelson model is restricted to drugs, which follow one-compartment open-model characteristics and in a way demonstrate the actual disposition of drugs after i.v. administration.
- ✓ This method has the advantage of not needing results from an i.v. reference standard.
- ✓ This model is usually not recommended for the analysis of data after oral administration of controlled delivery, which follow multi-compartmental disposition characteristics.
- ✓ The Wagner-Nelson model is given as follows;

$$(X_A)_T / (X_A)_\infty = C_T + Ke \int_0^T C dt / Ke \int_0^\infty C dt$$

- ✓ For many drugs, which are given as SR formulations and have a rapid distribution phase relative to drug absorption, the Wagner-Nelson model can provide a reasonable basis for the estimation of absorption parameters.

Model independent pharmacokinetic analysis

- The model independent disposition of the drug from a sustained release formulation is applicable in the situation when the drug is eliminated following linear formulation.
- By using statistical moment theory, one can calculate MRT after administration of standard and sustained release formulation.
- MRT is defined as the mean time for the intact drug molecule through the body tissue and involves a composite of all kinetic process including release from the dosage form drug absorption in to the body and drug disposition.

Cont...

- The MRT can be used in comparative to evaluate the in vivo performance of sustained release dosage form.
- Longer the MRT the more sustained or prolong is the absorption of the drug assuming a constant elimination rate constant.
- MAT is more relevant in assessing the absorption process than MRT.
- The longer the MAT the more sustained or prolonged is the absorption of the drug.

- MAT parameter can be used in calculation of apparent absorption rate constant in the case of first order absorption process and absorption time (T) in the case of zero order absorption process.

$$\mathbf{MAT = 1/K_a}$$

$$\mathbf{MAT = T/2}$$

Pharmacodynamic Models

Fixed effect model:

- ✓ The drug concentration can be related to a pharmacological effect which is either observed or not.
- ✓ The major draw back of fixed effect model is inability to relate a range of drug concentration to broad range of pharmacological effect.

Linear model:

- ✓ The most fundamental model directly linking drug concentration and effect.

$$E = P.C$$

$$E = P.C + E_O$$

- ✓ The parameter P estimated from $E-E_O$ versus C

$$E = P.\log C + E_O$$

Conclusion

- Pharmacokinetic and pharmacodynamic models help in understanding the various parameters involved with controlled release systems.
- They also help in designing specific requirements required for drug molecules to be formulated as controlled release systems, there by enhancing better opportunities for the development of controlled release systems in future.

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