MPH202T

(APPLICATIONS OF PHARMACOKINETICS)

MODIFIED RELEASE DRUG PRODUCTS

Most conventional (immediate release) oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration. In the formulation of conventional drug products, no deliberate effort is made to modify the drug release rate. Immediate-release products generally result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. In the case of conventional oral products containing prodrugs, the pharmacodynamic activity may be slow due to conversion to the active drug by hepatic or intestinal metabolism or by chemical hydrolysis. Alternatively, conventional oral products containing poorly soluble (lipophilic drugs), drug absorption may be gradual due to slow dissolution in or selective absorption across the GI tract, also resulting in a delayed onset time.

The pattern of drug release from modified-release (MR) dosage forms is deliberately changed from that of a conventional (immediate-release) dosage formulation to achieve a desired therapeutic objective or better patient compliance. Types of MR drug products include delayed release (eg, enteric coated), extended release (ER), and orally disintegrating tablets (ODT). The term *modified-release drug product* is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is a formulation in which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Several types of modified-release oral drug products are recognized:

1. **Extended-release drug products.** A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release (CR), sustained-release (SR), and long-acting drug products. **Sustained-release dosage forms** are dosage forms designed to release (liberate) a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. This can be achieved through a variety of formulations, including liposomes and drug-polymer conjugates (an example being hydrogels). SR maintains drug release over a sustained period but not at a constant rate. CR maintains drug release over a sustained period at a nearly constant rate.

2. **Delayed-release drug products.** A dosage form that releases a discrete portion or portions of drug at a time other than promptly after administration. An initial portion may be released promptly after administration. Enteric-coated dosage forms are common delayed-release products (eg, enteric-coated aspririn and other NSAID products).

3. **Targeted-release drug products.** A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

4. **Orally disintegrating tablets (ODT).** ODT have been developed to disintegrate rapidly in the saliva after oral administration. ODT may be used without the addition of water. The drug is dispersed in saliva and swallowed with little or no water.

The term *controlled-release drug product* was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery. Other terms, such as ER, SR, XL, XR, and CD, are also used to indicate an extended-release drug product. Retarded release is an older term for a slow release drug product. Many of these terms for modified-release drug products were introduced by drug companies to reflect a special design for an extended-release drug product.

Variables to consider for modified release dosage form:

1. Low dose

2. Short half life

3. Long half life drugs already have the desired kinetics

4. Wide Therapeutic Window

5. Absorbed through the entire GI

6. Modest to rapid absorption

7. Highly stable in the GI

8. Chronic treatment like Hormone Replacement, Hypertension, Chronic Pain, Allergies

Advantages:

1. Increased time within the Therapeutic Window due to lower peak plasma concentration and shallower slope

2. Has kinetics similar to IV infusion, with the ease of a tablet

3. Reduce dosing frequency

4. Improve patient compliance

5. Reduce gastric irritation and side effects

6. Possible to enhance the bioavailability

7. Alleviate the risk of dose dumping

8. Reduce fluctuation in circulation drug level

9. Avoidance of night time dosing

10. More uniform effect

Disadvantages:

1. If a toxic dose is given, it will stay toxic for a long time

2. Takes a long time to titrate patient

3. Strong first pass effect by staying below the metabolizing enzymes saturation point

4. Risk of Dose Dumping (failed delivery device) a large immediate dose

5. Inflexible dosing schedule

6. Can't usually split tablets Types of modified release dosage

Pharmacokinetic studies - The purpose of these studies is to characterize the modified release formulation in vivo by investigating:

• The rate and extent of absorption

• Fluctuations in drug concentrations at steady state

• Inter-subject variability in pharmacokinetics arising from the drug formulation

• Dose proportionality

• Factors affecting the performance of the modified release formulation

• The risk of unexpected release characteristics (e.g. dose dumping)

The studies are based on concentration measurements of the active substance and/or metabolite(s) or, occasionally, in conjunction with determination of an acute pharmacodynamic effect. Due to the substantial formulation impact the requirements about metabolites given in the "Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)" is not applicable in this case. Active metabolites should be measured since a change in absorption rate or route of administration may modify the extent and pattern of metabolism. The studies can be performed either in healthy volunteers or in patients in case of safety concerns. Whenever

multiple dose studies are performed it should be demonstrated that steady state has been reached. Achievement of steady-state is assessed by comparing at least three pre-dose concentrations for each formulation, unless otherwise justified. In case of no accumulation, multiple dose studies are not required.

Modified drug delivery system such as sustained or controlled release tablets and capsules generally consists of drug dispersed in a polymeric matrix where the process of diffusion predominates. Drug dissolution from solid dosage forms has been described by some kinetic models in which the dissolves amount of drug (Q) is a function of the time (t) or Q = f (t). Mathematical models commonly used to determine the drug release/dissolution profile are Zero order kinetics, First order kinetics, Hixon-Crowell, Higuchi model. Weibull model, Baker-Lonsdale model, Korsmayer-Peppas model and Hopfenberg model. Some other release parameter such as dissolution time, assay time, dissolution efficacy, difference factor (f1) and similarity factor (f2) can also used to characterize drug dissolution / release profiles.

While the Higuchi model had a large application in polymeric matrix systems, the zero order models becomes the ideal to describe coated dosage forms or membrane controlled dosage forms. The criterion to choose the best model to study the drug dissolution/release phenomenon is the use of the coefficient of determination (R^2), to assess the fit of a model equation. Usually, this value tends to get greater with the addition of more parameters, irrespective of the significance of the variable model.