GUIDELINES FOR THE DESIGN AND EVALUATION OF ORAL PROLONGED RELEASE DOSAGE FORMS

Ministry of Health and Welfare, Japan
(March 11, 1988)

In recent years, in association with progress and innovation in the field of pharmaceutical technology, there has been an increasing effort to develop prolonged release dosage forms for many drugs. Correspondingly, a growing number of new prolonged release dosage forms have been submitted for regulatory approval. Prolonged release dosage forms have many advantages in safety and efficacy over immediate release drug products in that the frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence and/or intensity of adverse effects can be decreased.

However, some prolonged release dosage forms have less clear rationale or are developed for active ingredients which are not appropriate for prolonged release dosage forms. In other cases, prolonged release dosage forms are designed without full consideration of the basic properties of the drugs. Moreover, standards for dissolution tests, which are important for evaluating prolonged release dosage forms, have not appropriately been established. As a result, it is often difficult to evaluate whether a prolonged release dosage form is acceptable or not. Incomplete or undesirable prolonged release drugs may merely cause therapeutic confusion and, in addition may interfere with development and spread of good quality drugs. As part of the effort to ensure and promote drug reliability, it appears necessary to establish appropriate guidelines for the design and evaluation of prolonged release dosage forms.

The present guidelines are prepared for oral prolonged release dosage forms, mainly for drugs with new pharmaceutical forms. However, many of the general principles of the guideline are also applicable to other controlled release dosage forms.

1. Factors to be studied in dosage form design

1. I The properties of the active ingredient

The following characteristics of drugs are critical in ensuring their efficacy and safety. Therefore they should be sufficiently studied to fulyl characterize the drug.

i) **Elimination half life**: Drugs with long elimination half lives are generally undesirable for prolonged release dosage forms unless designed to prevent toxic effects due to a peaking effect or to reduce the dose.

ii) **The first pass effect**: Bioavailability may be significantly impaired if the release

rate is retarded for drugs that suffer from an extensive first pass effect.

iii) **The absorption site**: If the absorption site is limited, absorption is likely to decrease and variable bioavailability will occur for typical prolonged release dosage forms.

iv) **Adverse reactions**: Undesirable adverse reactions may develop by using prolonging drug release.

It is desirable to clarify following factors:

i) Correlation of clinical response with blood-drug concentrations or tissue concentrations at the site of action.

ii) Induction or inhibition of drug metabolizing enzymes by the prolonged blood concentration, casual change of pharmacological response and the possibility of tolerance or addiction for the drug.

iii) Interactions with other drugs due to protein binding.

1. I. 1 Pharmacodynamics

The major purpose for developing prolonged release formulations of the drug is generally to maintain the blood concentration of the active ingredient at therapeutically effective levels. Therefore, it is desirable that average minimum effective concentration and optimal therapeutic concentrations be clarified for each drug by evaluating blood concentrations of the active ingredient or therapeutic moiety(s) including active metabolite(s) in relation to drug efficacy. The intra- and intersubject variations should be investigated for further confirmation of those levels. It is also desirable to investigate toxic blood drug concentrations.

If the effective blood drug concentration is not known, estimates should be made from dose levels, blood concentrations, and clinical data based on the immediate release drug product. If effective blood drug concentration is unclear, the usefulness of the prolonged release dosage form should be demonstrated by well-designed clinical studies.

1. I. 2 Biopharmaceutics

Information on the biopharmaceutical properties of the active ingredient for a prolonged release dosage form is essential in rational formulation design. Particular attention should be given to the following six factors: 1) location of major absorption sites or specificity in the site of absorption, 2) absorption rate, 3) the elimination half life of the drug, 4) whether absorption is non-linear due to the saturated drug absorption, first pass effects, or other reasons, 5) whether elimination is non-linear due to drug

metabolism saturation or other factors, and 6) inactivation or metabolism of the drug in the body, including the gastrointestinal tract. The above points should be clarified in humans if possible, or in animals if the evaluation in humans is difficult.

It is also desirable that the effect of food, drugs likely to be used concurrently and physiological factors such as renal or hepatic function on the absorption, distribution, metabolism and excretion of the drug be studied and evaluated.

In addition, it is useful to study effects of age, sex and smoking on the pharmacokinetics of the drug.

1.1.3 Chemistry and physicochemistry

Chemical and physicochemical properties of drugs, especially, pH- solubility characteristics should be clarified.

1.2 Factors due to physiological condition

The release of an active ingredient from a prolonged release dosage form, and its absorption are inevitably affected by physiological factors in the gastrointestinal tract. Prolonged release dosage forms are more susceptible to these factors than immediate release dosage forms. Therefore, the possible effects of the physiological factors should be fully considered for the dosage form design. If the drug is intended for use in a specific subpopulation, attentions should be paid to the specific physiology of the subpopulation.

1 .2.1 Transit characteristics of the dosage form through the gastrointestinal tract

The transit rate of a dosage form through the gastrointestinal tract is known to depend on the formulation properties such as size, form, specific gravity and adhesiveness of the preparation and physiological properties such as the length, size and motility of the gastrointestinal tract; and on the composition and volume of the gastrointestinal content. It is also affected by food, diseases, posture, and stress. The bioavailability of drugs often depends on the gastrointestinal transit rate of the dosage form. Therefore, the traveling characteristics of the dosage form through the gastrointestinal tract should be fully considered in designing advantageous dosage forms.

1.2.2 Physiology of the gastrointestinal tract

The physiological characteristics of the gastrointestinal tract (the volume, composition, pH, surface tension and viscosity of the gastrointestinal content; and gastrointestinal motility) vary greatly from site to site. Prolonged release dosage forms remain in the

gastrointestinal tract longer than conventional preparations. Therefore, physiological conditions of the gastrointestinal tract can affect the release of active ingredients of these forms much more than release from conventional forms. Noteworthily, gastric pH varies from acidic to neutral, and these variations can affect release of the active ingredient from the dosage form. These points should be considered when a formulation is being designed and assessed.

1.3 Prototype dosage forms and selection of the final dosage form

Desirable criteria of performance for prolonged release dosage forms are: duration of appropriate blood drug concentration for a sufficient time with minimal influence of food and physiological conditions of the gastrointestinal tract; and minimal contribution to intra- and intersubject variation. To select the best possible dosage form, all candidate forms should be fully tested for release characteristics. Moreover the pharmacokinetic profile should be evaluated in an appropriate species of animal or volunteer.

2. Factors to be studied in the final dosage forms

2.1 Evaluation of the final dosage form

2. I. 1 Release characteristics

A. Evaluation of the release characteristics

The release of the active ingredient from the preparation in the gastrointestinal tract is affected by many physiological factors including the mechanical force exerted by the digestive tract in relation to its movement, and the volume, composition, pH, surface tension, and viscosity of the gastrointestinal fluid. Therefore, the in vitro release behaviors should be investigated under as many conditions as possible to understand possible effects of gastrointestinal variables on in vivo release. To achieve stable blood concentrations, it is generally desirable to prepare prolonged release dosage forms whose release rates are minimally pH dependent. Therefore, release of the active ingredient should be evaluated at multiple levels of pH, such as 1.2, 4.0 and 6.8, representing typical gastrointestinal pH variation. Considering the variation in gastrointestinal motility; agitation rates should also vary more than 2 levels among 50, 100 and 200 rpm, when the paddle method is used, at an appropriate pH. If it is anticipated that the release rate is influenced by the wettability, ionic strength and composition of the test medium, their effects should also be investigated. It is also desirable to perform release tests using different kind of apparatus.

On the other hand, taking into consideration the variation of mechanical stress in

the gastrointestinal tract, the drug release from prolonged release dosage forms containing an active ingredient with a narrow therapeutic window should be tested by the methods having a high mechanical stress, such as JP disintegration test method, the rotating flask method using beads and solubility simulator.

B. Specifications for dissolution testing

The specifications for drug releases should be established for quality control of prolonged release dosage forms. Basically, it is desirable to employ the release tests which can predict the blood level profile of the drug as precisely as possible. It is also desirable to set the specification including sampling time and amount of drug to be released so as to show the release profile as accurately as possible. The tolerable range of the drug release change depending on the effect of the release rate on absorption or a related pharmacodynamic property (therapeutic window, toxicity or adverse reactions). Therefore, based on the relation between release rate and blood concentration or pharmacological effects, the tolerable range should be set within limits which do not allow great changes in blood concentrations or in clinical efficacy. The narrow tolerance limits should be set as much as possible to decrease the variation in drug release which will provide stable clinical effects.

If the relation between the release rate and blood concentration is not clear, or if sufficient data are not available to prove the correlation, it is difficult to set rational specification. In such a case it is desirable to set specifications using the second method (paddle method) in the Japanese Pharmacopoeia at sampling time points of 20-40%, 40-60%, and more than 70% of the labeled amount of the active ingredient is released. If 100 rpm and 900 ml of test fluid was used for the paddle method, the tolerance ranges at 1st, 2nd and 3rd points should be set within ±15%, ±15% and ±10% of the average release, respectively. At the 3rd sample point, only lower limit is acceptable instead of the tolerance range. The acceptance criteria of the drug release follow the criteria of dissolution or release tests of JP XI or USP XXI.

C. Stability test

Specimens for long term stability tests should be subject to dissolution testing and comply with the standards of the specifications.

2.1.2 Pharmacokinetics

A. Comparison of the prolonged release dosage form with an immediate release dosage form

As far as possible, the pharmacokinetics of the prolonged release dosage form should be compared with the immediate release product in healthy volunteers. Pharmacokinetic

evaluation should be made, based on blood concentration data, except for the case that the concentrations of the active ingredient can be determined at the site of action whose effective concentrations are known. Data on drug concentration in the urine, saliva, or other body fluids will be accepted only when the concentrations of the active ingredient in the blood or at the site of action are correlated with that in these fluids.

Unless the drug shows linear pharmacokinetics within the clinical dose range, the investigation should be made at two dose levels, high and low.

i) Single dose study: The usefulness of the new prolonged release dosage form given according to the dosage regimen should be evaluated by comparing the blood concentration with that of the immediate release dosage form or alternative forms such as solution or a powder; or with a prolonged release product which has already been approved, when better prolonged release characteristics are claimed. The parameters to be compared are AUC (zero to the final sampling time), AUC (0-∞), Cmax, the duration of the minimum effective concentration, or optimal effective concentrations of the active ingredient if these concentrations are known or can be estimated. It is desirable to determine the time to reach the minimum effective concentration or the optimal effective concentration, Tmax, absorption rate constant, elimination rate constant, clearance, extent of absorption and MRT and VRT by the moment analysis method.

ii) Multiple dose study: Prior to a multiple dose study, a blood concentration profile at steady state for multiple dosing of both standard and test dosage forms should be simulated from the single dose pharmacokinetic trials. In the multiple dose studies, it should be ascertained that Cmax and Cmin at steady state are within the estimated ranges, and the usefulness of the prolonged release dosage form should be evaluated by comparing it with the reference product in 1) Cmax, 2) Cmin, 3) the difference between Cmax and Cmin or the ratio (dosage form index, Cmax/Cmin), and the duration of the minimum effective concentration or that of optimal effective concentration. For drugs with non-linear absorption or elimination, those with a narrow therapeutic window, or those which may cause severe adverse reactions, the blood concentration profile at steady state should be characterized by multiple dose studies. When multiple dose studies in healthy volunteers are not done, the usefulness of the prolonged release dosage form should be shown using the simulated parameters, where it is necessary to confirm that Cmax and Cmin are within the predicted range, by monitoring blood concentrations in clinical studies.

B. Effect of dosing conditions and physiological factors

Factors which might affect the pharmacokinetics of a prolonged release dosage form should be studied in which food is particularly an important factor because it is know to affect transit of dosage forms in gastrointestinal tracts, disintegration, and release of the drug. Therefore, the blood concentration profiles of the prolonged release dosage form should be compared between fasting and fed conditions. If a significant effects of food was observed, a special caution should be included in the dosage regimen (i.e. indication of drug administration only after meals), and it should be clarified whether the food effect was related to the drug itself or dosage forms by performing similar food studies using the drug solution or the immediate release product, although the studies are not needed when there is published evidence. In addition, as far as possible, it is desirable to clarify other factors of food (e.g., the volume and composition of meal, and intervals between food and drug administration) affecting the in vivo release and absorption.

It is also desirable to investigate diurnal variations of pharmacokinetic parameters.

2.1.3 Clinical efficacy

The clinical usefulness of the prolonged release dosage form should be shown comparing it with its already approved immediate release product or its already approved prolonged release product (if a better prolonged release dosage form is claimed).

If the relation between the pharmacological effectiveness and blood concentration is unclear, the usefulness should be proved by the well-controlled clinical studies where the effective and toxic concentrations should be investigated by monitoring blood concentrations of the drug.

2.2 Establishment of dosing regimen

The appropriate dosing regimen should be established during Phase I and 11 clinical studies in which it is recommended that the blood concentrations are monitored during Phase 11 clinical trials to establish a better dosing regimen.

2.2.1 Factors of particular importance in establishing dosing regimen

i) Overdose or dose dumping: Sustained release dosage forms might be more likely to produce significant adverse and toxic effects than immediate release dosage forms in case of overdose or dose dumping because of the higher doses of active ingredients which are absorbed over a prolonged time. Dose dumping,

e.g. resulting from crushing by the teeth, may be another problem with prolonged release dosage forms. This is of particular concern for drugs with a narrow therapeutic window, and so studies are desired to establish preventive measures and actions to be taken in such cases.

ii) Disease state: The physiological changes in gastrointestinal tract, liver, kidneys, or heart due to diseases often affect absorption, distribution and elimination of drugs and there is a possibility that prolonged release dosage forms are particularly susceptible to the changes. In such cases, the dosing regimen should be studied and established as to reflect the pathological changes.

iii) Combination therapy: If any other drug is used concurrently, it may affect the absorption, distribution, and elimination of the drug contained in the prolonged release dosage form. As a result, blood concentrations of the drug may be changed, and this may affect the efficacy. The possible effect of drugs which might be used together in practice should be studied, and suitable indications and special warnings for the concurrent use of other drugs should be established.

2.2.2 Dosing guidelines

Recommendations for dosing conditions, frequency of dosing per day, and dose levels (initial dose, maintenance dose, dose adjustment for insufficient response, and the maximum tolerable dose) should be established, based on the available pharmacokinetic data during Phase 11 clinical studies. The action to be taken if toxic signs or adverse effects develop should also be specified in these guidelines.

Detailed dosing guidelines including information about dose adjustment based on blood concentration monitoring or changes in renal clearance of each patient may be useful to maximize the therapeutic efficacy by making the utmost use of the advantages of the prolonged release dosage form.

It is desirable to set up corresponding detailed guidelines particularly for prolonged release products containing A) drugs, blood concentrations of which may change strikingly by minimal changes in dose (drugs with non-linear absorption or elimination), B) drugs, the clearance and blood concentrations of which are susceptible to physiological conditions, age and so forth, C) drugs with a narrow therapeutic window, and D) drugs which might cause tolerance and/or severe adverse effects.