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A proposed general protocol for testing bioequivalence of controlled-release drug products

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Summary

This paper proposes methods to test whether marketed or newly developed controlled-release drug products are functioning in the manner indicated by the formulation and product literature. Typical controlled-release preparations are supposed to release part of the dose immediately, the amount should be essentially consistent with a conventional release single-dose product, and the rest of the dose at a constant (zero-order) or nearly constant rate. These release patterns can be effectively evaluated by calculation of a controlled-release effectiveness (CRE) parameter and an absorption rate effectiveness (ARE) parameter described herein.

Introduction

A large number of orally administered marketed drug products are being tested for marketing as controlled-release products. The term "controlled-release" implies that some modification is made upon the dosage form to develop a longer-acting oral dosage form (Ritschel, 1973). One classification of these dosage forms advocates 3 basic types of controlled-release products: (1) sustained release; (2) repeat action; and (3) prolonged action dosage forms (Ballard, 1980). Formulating drugs into these types of systems has been described as having a two-fold advantage: it is a convenience to the patient in reducing the number of doses while improving compliance, and it improves therapeutic management by provision of more constant plasma levels of the drug. Ideally, a candidate drug for controlled-release will be a chronically administered product having a relatively short elimination half-life and a clearly defined minimum therapeutic concentration (Gibaldi and Perrier, 1975). Also the dose should be relatively small with the drug being well absorbed throughout the gastrointestinal tract. A recently published book provides a framework for assessing

a specific drug's candidacy for a sustained (controlled) release system (Robinson, 1978). In addition, the book provides a plan of attack to use in formulation of such drug delivery system.

Few discussions of solely bioequivalency or methods to access bioequivalency, between different formulations of a drug in controlled-release products exists in the literature. Bioequivalency of such products is not as clearcut as bioequivalency of standard regular-release drug products because of the variation in product construction. Additionally there seems to be somewhat different approaches to the controlled-release formulation with regard to how it should dissolve and be absorbed in vivo. However, the clinician (and patient) expects the therapeutic (and pharmacokinetic) activity to remain unchanged. Also, it is of value to know how effective a controlled-release product is compared to the blood levels produced by a regular release formulation of that drug.

This manuscript describes some of the more important dosage form parameters, obtainable from both in vitro and in vivo investigations and describes how these parameters can be used for the evaluation of controlled-release drug products. These parameters should apply to both innovator and generic controlled-release dosage forms.

Background

While the advantages of controlled-release dosage forms are reasonably established, the approaches to providing this type of drug release produces a widely divergent array of products (Ritschel, 1973). This fact coupled with the wide inter- and intra-subject variability found in gastric transit time, drug absorption, and bioavailability parameters in general, has given rise to much indecision regarding the utility of and the means to evaluate such dosage forms.

The Food and Drug Administration requires that controlled-release drug products deliver the drug as claimed (i.e. in a "controlled" manner, which precludes the possibility of any dose-dumping effects). In addition the agency requires these products to provide steady-state performance comparable to marketed non-controlled release products given in multiple doses (of an equivalent daily amount), and to produce consistent pharmacokinetic performance between individual dosage units (Federal Register, 1977).

An examination of the literature yields a considerable number of references dealing with controlled-release products but few dealing with product or interproduct evaluation. Wagner (1971) cites over 150 references on controlled-release drug products. Within the text on controlled-release products Robinson cites a large number of articles with regard to pharmacokinetics after controlled-release product administration and strategies for developing of such products, but few articles dealing with in vitro and/or in vivo test methodologies. The Ritschel review discusses the theoretical release of drugs from various types of controlled-release dosage forms. Sjogren (1971) has discussed the difficulties of using in vitro methods to evaluate the performance of this type of product. He noted the need for

reproducibility of in vitro methods as well as the need for caution in the application of such data. A number of in vitro methodologies have been used as a means of evaluating controlled-release preparations; most of these methods have ignored the necessity of correlation with in vivo parameters (Wagner, 1971).

Since most articles dealing with controlled-release concentrate solely on pharmacokinetics, in vitro release rates, or types of construction (and as Gibaldi and Perrier point out, there are relatively few zero-order release products on the market), there is a paucity of information relating to methods for assessing the achievements of the product. How should a drug product not previously manufactured as a controlled-release product be assessed? How does the new product compare versus the regular-release product? Should the new controlled-release product be compared to multiple doses of regular product? Should in vitro assessment be carried out? What goals and parameters should be measured? If different types of controlled-release construction for the drug are already on the market, how should a new controlled-release form of the same drug be assessed? Is in vitro testing alone sufficient? Should the regular-release product be included in in vivo and/or in vitro (cross-over) studies?

Theoretical

The first step in the assessment of controlled-release products must start with a statement of the therapeutic goal of the controlled-release product. This statement is best formulated in terms of a desirable, or an effective, or a therapeutic blood level of the drug entity. In most cases the blood level goal for the controlled-release product is compared to blood levels obtained from a non-controlled (regular) release product given sequentially.

In this paper two parameters are suggested for evaluating the controlled-release product: (1) the length of time a controlled-release product maintains a desirable (effective, therapeutic) blood level actually quantitated via an area measurement; and (2) the rate with which the controlled-release product reaches the desirable (effective, therapeutic) blood level.

The assumptions associated with these evaluation parameters are as follows.

(1) The desirable (effective, therapeutic) blood level is defined as a concentration range varying from the trough level, reached just prior to the time when the second dose of that product is normally given, to the maximum concentration observed, generally following the second dose of the regular release product. Alternatively this range may be the known therapeutic range for the drug entity.

(2) A correlation exists between the dissolution rate of the drug product (controlled release or regular release) and the apparent absorption rate of the product, as measured by in vivo studies.

Fig. 1 illustrates the parameters utilized in this study. C_{min} is the initial blood level trough in a sequential administration of a regular release dosing regimen. C_{max} is the maximum blood level for a sequentially administered regular-release product (or steady-state concentration, in multiple dosing studies). R_{aa} is an apparent

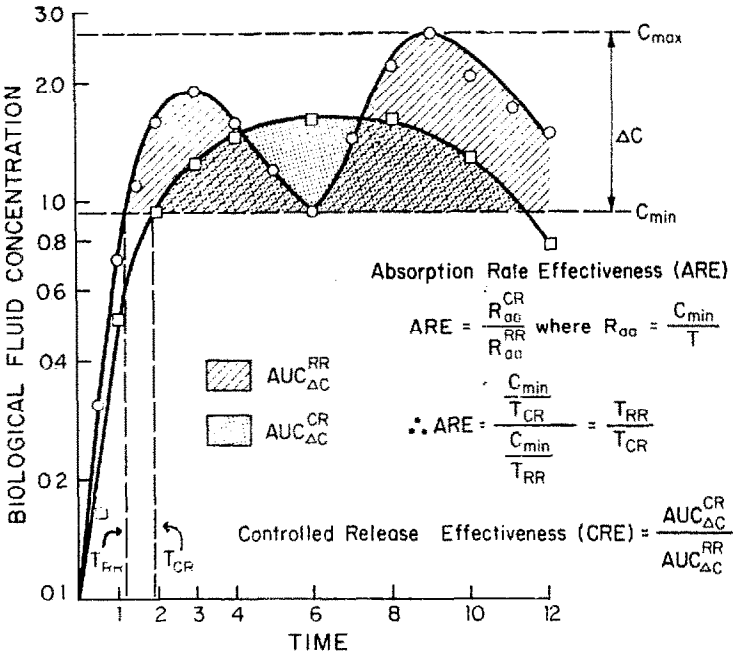

Fig. 1. Comparative curves for regular-release (RR) drug product (administered at 0 and 6 h) and controlled-release (CR) product (administered at 0 h) showing the respective areas under the curves above and below C_{min} and C_{max}, respectively. The C_{min} and C_{max} are obtained from the regular-release product administered twice; see text. Also the times the two products reach C_{min}, involved in determination of absorption rate effectiveness, are shown.

absorption rate based on in vivo studies which measures the time necessary for a given dose of drug to first reach a C_{min} blood level concentration.

$AUC_{\Delta c}$ is the area under the blood concentration–time curve within the desirable (effective, therapeutic) blood concentration range (see Fig. 1). The superscript refers to controlled release (CR) or regular release (RR) product. The $AUC_{\Delta c}$ value measures the area under the blood concentration–time curve only within the desirable (effect, therapeutic) concentration ranges of the drug. Therefore, the area below or above the desirable range is not included in the evaluation of drug effectiveness. Area above C_{max} in the controlled-release product can be used to measure "dose-dumping" for a product. The area below C_{min} is assumed to be therapeutically ineffective. Therefore, controlled-release products which show equivalency in total amount absorbed to a regular-release product may be completely ineffective therapeutically because blood levels never reach C_{min}, in the beginning of a hypothetically desirable blood level.

An important estimate of product effectiveness would be the determination of the CRE (controlled release effectiveness) defined as the ratio: $CRE = AUC_{\Delta}^{CR}/AUC_{\Delta c}^{RR}$. Values close to 1 indicate that a single dose of a controlled-release product is equivalent to multiple-doses of the regular-release product. CRE can be a useful parameter for the assessment of controlled-release product efficiency.

Another parameter useful for the comparison of controlled-release to regular-re-

lease products is the ratio of times taken to reach the C_{min} here designated R_{aa}. The term R_{aa} is calculated for the controlled-release (CR) and regular-release (RR) product as follows:

$$R_{aa}^{CR} = \frac{C_{min}}{T_{CR}} \text{ and } R_{aa}^{RR} = \frac{C_{min}}{T_{RR}}.$$

Thus the absorption rate effectiveness (ARE) may be determined as the previous ratio: $ARE = R_{aa}^{CR}/R_{aa}^{RR}$ which may be further reduced to:

$$ARE = \frac{\frac{C_{min}}{T_{CR}}}{\frac{C_{min}}{T_{RR}}} = \frac{T_{RR}}{T_{CR}}$$

Again, values close to 1 indicate that a single dose of a controlled-release product reaches effective concentration in blood at the same rate as the first dose of a sequential regimen of a regular-release product.

The overall effectiveness of the controlled-release product (E) (effectiveness) is the weighted sum of the two effectiveness parameters: E = a(CRE) + b(ARE), where a and b are the weights (a + b = 1) placed upon each of the effectiveness parameters based upon the goals outlined for the development of the controlled-release product. This implies then, that based upon a specific drug's best use, a specific indication or therapeutic response desired, or a company or individual policy decision, the a and b terms may not be 0.5 in all instances.

The actual procotol to be used in controlled-release dosage form assessment would be dependent upon one of the following premises.

(1) The controlled-release dosage form is a new product. Assuming that a drug product currently marketed in regular-release form meets the criteria for development of a controlled-release oral system (e.g. see Robinson (1978) or Wagner (1971)) certain procedures need to be performed. The assessment must be completed via an in vivo protocol. A two-way cross-over study, in human subjects, comparing the controlled-release product (single dose) with the regular-release product is necessary. Since one has the expected modification of blood levels and the length of time of the dosing interval for the controlled-release product in mind, the controlled-release product should be compared to an equivalent administered amount of the regular-release product, consistent with the usual dosing of the regular-release product. That is, the regular release product may be administered at 0 and 6 h (i.e. a normal Q6H product) and this may be compared to the controlled-release product given at 0 h (i.e. a Q12 H product).

If the initial single dose of the regular-release product produces blood levels greater than the minimum effective concentration (this is not likely since most drugs accumulate to some extent and a number of doses must be taken for effective and steady-state levels to be reached), then this concentration can be used to assess the controlled-release effectiveness, as shown below. If a minimum effective drug

concentration is not attained, the minimum at 6 h (i.e. trough level just before the subsequent dose of the Q6H drug) should be chosen for assessment of controlled-release effectiveness. Alternatively, some arbitrary drug concentration may be examined for the lower range. Additionally a C_{max} can be defined as the maximum concentration measured, most likely after the second dose (given at 6 h) of the regular-release product. These two concentrations are used to determine the effectiveness of the controlled-release product based on the cross-over study over the 12 h.

The controlled-release effectiveness (CRE) may be assessed by calculation of AUCs above C_{min} and below C_{max} for both products as shown in Fig. 1. ΔC is simply the range from C_{min} to C_{max}. The areas within this range for both products are calculated and the CRE is reported as a ratio. Fig. 1 also shows the R_{aa} parameter for both dosage forms. This is simply the time taken to reach the C_{min} for both products. The absorption rate effectiveness (ARE) may be calculated from these times.

(1a) The controlled-release dosage form is a new product and the manufacturer whishes to conduct multiple dose studies. Such studies may confirm data gathered in the single-dose studies above and thus may be considered proof that the controlled-release product is effective; however, such multiple-dose studies should not be obligatory. The indicating ratio, CRE, may be obtained from steady-state dosing studies using similar C_{min} and C_{max} concentration limits of the regular release dosage form, here usually referred to as C_{min} and C_{max}. Likewise CRE ratios of approximately 1.0 would indicate an effectively formed controlled release dosage form.

While one or both of the above in vivo studies are being performed in vitro dissolution studies should also be examined. Such studies can be designed to determine the dissolution method and experimental conditions providing significant correlation with the in vivo behavior The development of an in vitro dissolution specification which would show correlation with the in vivo result requires the use of several dissolution apparatuses and variable conditions, e.g. media, agitation, etc. (Needham and Luzzi, 1974; Needham et al., 1978). Initial work in these laboratories has shown that statistically significant and physically meaningful correlations or comparisons between in vitro–in vivo data can be made if one examines the rate to peak (both peak blood level (C_{max}) and maximum amount dissolved) instead of the absolute absorption rate (k_a), which may be hard to assess with many experimental protocols. The in vivo data must be transformed from blood level–time data to fit a model for any upward sloping asymptotically limited curve, e.g. $C = L\ (1 - e^{-kt})$ where C is the concentration, L is the limit (either amount in dosage form, or the C_{max}), and k is the rate constant reflecting release of drug (in vivo and in vitro). Making these rates equivalent, rate to maximum amount dissolved and rate to maximum blood level, enables comparisons to be made. Although the usual methods of correlating in vivo–in vitro parameters of selected controlled-release drugs uses a comparison of percent dissolved with percent absorbed (Graffner, 1974), a more physically meaningful and generally applicable correlation would be the rate to peak blood concentration vs dissolution rate, or AUC vs dissolution rate, or peak blood concentration vs drug dissolved at various times, albeit a sound dissolution in

controlled-release dosage form manufacture and modification.

(2) A generic controlled-release product is proposed and insufficient information is available on dissolution specifications used by the innovator. If these are the conditions which exist, it would be imperative that the prospective manufacturers conduct an in vivo study as described above (1). In addition, the dissolution testing method, as outlined above, should be generated with the appropriate correlations made (i.e. rate to peak in vivo vs rate to peak dissolution, etc.).

Fig. 2 is a theoretical representation of what most successfully formulated controlled-release products would look like when compared to multiple (two) doses of regular-release drug product. As stated previously some controlled-release products may not look like this even in the ideal case since diurnal variation or other physiological factors may play a role. Fig. 2 depicts the situation where the C areas for both products would be approximately equivalent as well as being the absorption rate effectiveness parameter. The inset in Fig. 2 depicts a poorly formulated controlled-release product.

Application

Applying the above methods to previous reports by the authors for chlorpheniramine controlled-release and regular tablet dosage forms (Kotzan et al., 1982) yields approximately what would have been predicted for these controlled-release

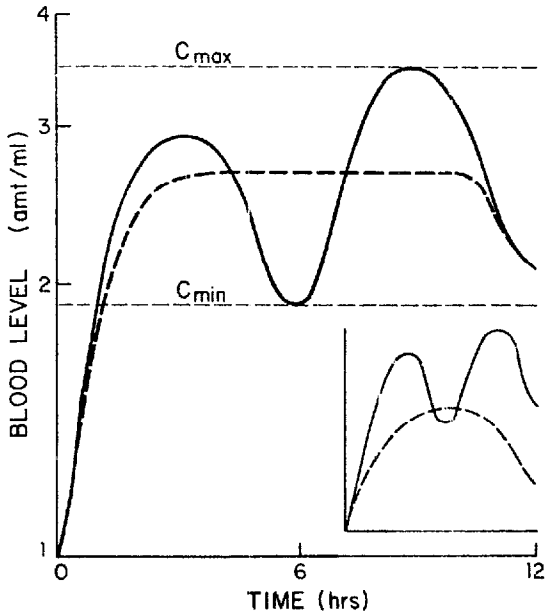

Fig. 2. Theoretical ideal performance from an oral controlled-release dosage form compared to two regular release administrations (at 0 and 6 h); CRE = 1.0. Inset shows a poorly formulated controlled-release drug product, here CRE is very small (< 0.1). The assumption is made that the total dose is equivalent (e.g. 50 mg of regular-release product at 0 and 6 h and 100 mg of controlled-release product at 0 h).

dosage forms of chlorpheniramine. The 4 mg chlorpheniramine tablet, given at 0 and 6 h, gave a minimum of 3.8 ng/ml at 6 h; this was the C_{min} used. The C_{max} from the 4 mg tablet occurred 2 h after the second dose (i.e. at 8 h time elapsed). Calculation of the CRE (controlled release effectiveness) based on areas above and below C_{min} and C_{max}, respectively, for the two controlled-release products studies gave the following results (for data see Kotzan et al.). 2×4 mg tablet, $AUC_C^{RR} = 26.425$ ng · h/ml

8 mg coated bead product, $AUC_{\not C}^{CR} = 12.690$ ng · h/ml or CRE = 0.48

8 mg repeat action tablet, $AUC_{\not C}^{CR} = 17.205$ ng · h/ml or CRE = 0.65

As previously mentioned the optimum or highly desirable CRE and ARE should be near 1.0. Both chlorpheniramine controlled-release products studied gave decreased CRE values since their initial release was delayed (moreso in the coated bead product than the repeat action). The calculated ARE for these products are 0.45 for the coated beads and 0.38 for the repeat action tablet. The effectiveness, E, of these controlled-release products, assuming the weights are equal (i.e. a = b = 0.5), are E = 0.47 for the coated bead product and E = 0.52 for the repeat action tablet.

Examination of the literature produces a number of reports dealing with procainamide slow-release (i.e. controlled release) dosage forms (Dahl et al., 1976; Arstila et al., 1974; Graffner et al., 1974). Graffner et al. (1975) employed a protocol where procainamide slow-release was administered every 8 h and regular release every 4 h. Although the raw blood level data were not given, estimates of CRE were made from their figures after single dose administrations (i.e. 0 h for controlled-release product 0 and 4 h for regular) and multiple-dose administration, at the steady-state. The computed CRE is given below for the single-dose administration.

Procainamide, regular release tablet, $AUC_{\not C}^{CR} = 155$ μg · h/ml

Slow release, tablet A, $AUC_{\not C}^{CR} = 141$ μg · h/ml or CRE = 0.81;

and for the steady-state case,

Regular tablet, $AUC_{\not C}^{RR} = 176$ μg · h/ml

Slow release, tablet A, $AUC_{\not C}^{RR} = 162$ μg · h/ml or CRE = 0.92.

The ARE ratio appeared to be near 1.0—in both cases. It can be readily seen from this estimate of the data that the slow release formulation (table A) was approaching a theoretically completely effective controlled release of procainamide, and that good agreement of CRE from single- and multiple-dose studies resulted. The effectiveness, E, for the procainamide products appears to be about 0.95 following single or multiple dosing of the controlled-release drug. It should be pointed out, however, that in both the single- and multiple-dose studies the C_{min} and C_{max} used to compute CRE were obtained from the regular release minima (before second dose administered). This is so even though procainamide is a drug with a well defined therapeutic range of 4 to 10 μg/ml (Koch-Weser and Klein, 1971). At the doses used in their work Graffner et al. administered 3 g/day (i.e. 500 mg Q4H or 1000 mg Q8H). The procainamide blood levels reported agree well with the other workers using similar dosing (Dahl et al. 1976; Arstila et al., 1974). This implies that to be in the therapeutic range more drug would have to be administered; the subtherapeutic problem does not lie in the dosage form.

Conclusions

There is a great level of current interest in controlled-release drug delivery systems. This most likely results from a desire for better therapeutic efficacy. With the increased interest in manufacture and marketing of oral controlled-release products should also come an increase in research methodologies used to formulate and evaluate such products. Some ideas for formulation strategies have recently been published along with the pharmacokinetic considerations involved in such product design (Robinson, 1978). This paper proposes methods to test whether a newly developed controlled-release product is functioning in the manner indicated by the formulation and product literature. It has been claimed that controlled-release preparations should release part of the dose immediately (the amount should be essentially consistent with regular-release single-dose product) and the rest of the dose at a constant (zero-order) rate (Nelson, 1957; Robinson and Eriksen, 1966; Dobrinska and Welling, 1975). This concept can be evaluated in practice by calculation of the controlled release effectiveness (CRE) and absorption rate effectiveness (ARE) described herein.

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