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CONTROLLED-RELEASE MULTIPLE-UNITS AND SINGLE-UNIT DOSES
A Literature Review.

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ABSTRACT

The strong influence exerted by the greatly varying normal gastrointestinal functions on the therapeutic value of a controlled-release single-unit dose is elucidated by a review of the literature. In this setting, the multiple-units dose comprising hundreds of mini-depots presents a highly preferable alternative which is due to a greater predictability and reproducibility of its therapeutic effect as well as a lowered risk of side effects.

INTRODUCTION

Sustained release, prolonged action, and repeat action are designations that characterize oral pharmaceutical formulations, each with a particular kind of prolonged and/or delayed drug release (1). These designations have, however, similar to several other less clearly characterizing terms such as slow release, timed release, and delayed release, been used indiscriminately for so long that they may be replaced by the

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common designation *controlled release* without further loss of meaning.

The term controlled release is thus satisfactory in as much as it solves the problem of a confused nomenclature, but it does, however, not reveal whether each dose is formulated to remain one undisintegrated unit, or whether it is composed of a large number of mini-depots (sub-units) dispensed in a capsule or a tablet. In our opinion, a clear distinction must be made between these two formulations, and to serve this purpose the future use of the terms *single-unit dose* and *multiple-units dose*, respectively, is proposed (2).

Mainly based on a review of the literature, the differences between them, pharmaceutical as well as clinical, will be pointed out, and it will be emphasized that in many cases it is highly important to know whether a product is a single-unit or a multiple-units formulation.

DEFINITIONS AND PREREQUISITES FOR ORAL DEPOTS

A single-unit dose, e.g. a matrix tablet or a tablet enclosed in a diffusion membrane, is a depot which releases a drug during the passage of the entire alimentary canal without disintegrating. The empty core or shell is discharged (3). To retain a depot effect it is imperative that the dose unit is swallowed intact (4,5) as dividing it would result in an unintended rapid drug release (6).

A multiple-units dose consists of many mini-depots, e.g. pellets or microencapsulated crystals contained in a capsule or a tablet. These hundreds of mini-depots are dispersed and distributed throughout the gastrointestinal tract when the capsule or tablet disintegrates (7,8,9,9a). A multiple-units tablet may thus be divid-

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ed at ingestion without loss of the depot effect, as the sub-units act as self-contained depots (10), Table 1.

Not every active agent lends itself to a controlled-release formulation (5,11,12). This may be due, partly to physical-chemical conditions, partly to pharmacokinetic, pharmacological, or toxicological features of the drug, and the considerations required in this context are to a large extent independent of whether the depot preparation being contemplated is of the single-unit or the multiple-units type.

On the other hand, the difference as regards attaining a reproducible therapeutic effect may be considerable, as the effects of a single-unit and a mul-

TABLE 1.

SINGLE-UNIT DOSE	MULTIPLE-UNITS DOSE
Definitions	
Oral pharmaceutical formulation consisting of one undisintegrating unit.	Oral pharmaceutical formulation consisting of a unit which disintegrates in the stomach into a large number of sub-units.
Examples	
Enteric-coated tablets passing undisintegrated through the stomach.	Capsules containing hundreds of pellets or thousands of crystals individually coated (enteric or timed-release) being dispersed upon disintegration.
Timed-release coated tablets, matrix tablets, etc. passing through the entire alimentary canal.	Tablets containing thousands of individually coated crystals being dispersed upon disintegration.

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tiple-units dose are not equally dependent on physiological functions like gastric emptying and intestinal motility.

THE INFLUENCE OF GASTRIC EMPTYING AND INTESTINAL MOTILITY

Gastric emptying is subject to both neural and hormonal regulation apart from being influenced by factors like the degree of distension, composition and viscosity of the stomach contents as well as pH and temperature (13,14).

Due to the multitude of causes, both the intra- and inter-individual variation is large. Unaffected by external influence gastric emptyings may take place at intervals of ½-10 hours (15). In addition, drug actions may come into play. Thus gastric emptying is inhibited by anticholinergics and narcotic analgetics while enhanced by metoclopramide (16).

The large variability of gastric emptying may have a deleterious influence on the reproducibility of the therapeutic effect of a drug as reported for l-dopa and digitoxin (17,18). In many cases not only the rate but also the extent of bioavailability is affected (16,19) and, of course, the more so when the formulation of the drug requires a proper complete gastric emptying for its pyloric passing, i.e. when the drug can be present *either* in the stomach *or* in the small intestine exclusively.

This is exactly the case of the controlled-release single-unit dose which having considerable dimensions (10-16 mm in diameter) is unable to reach the small intestine independently of gastric emptying. Accordingly the emptying of undisintegrated tablets from the stomach shows variations ranging from less than ½ to more than 7 hours (20,21).

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As many drugs show optimum absorption in the upper small intestine, a lasting detention of the dose in the stomach might imply a severely delayed absorption. According to Heading *et al.* the rate of absorption in man is directly related to the gastric emptying rate (22). An additional delay may occur if the amount of drug released in the stomach is diluted by becoming intimately mixed with, and possibly adsorbed to, the bulk of food (23).

If the drug release from the depot is pH-dependent, e.g. low in an acid environment, the release process will only get properly started when the depot is emptied into the intestine. Also in this case the bioavailability rate will depend closely on gastric emptying, and the reproducibility of the effect is rendered questionable (24).

A particular disadvantage connected with the inclination of single-unit depots to be trapped in a narrow passage is constituted by the risk of local irritation or erosion when the released agent concentrates at the site of the trap. This risk attracted special notice in the case of potassium chloride (25,26,27), and it should now present a significant reason for refraining from formulating local irritants as single-unit depots.

Application of the multiple-units dose principle will essentially eliminate the dependence of the drug effect on gastric emptying, the mini-depots being sufficiently small (diameter <1 mm) to make possible their passage through the pylorus even between its actual openings (7,8,9).

As a result of this, i) the drug may reach the site of optimum absorption in a reproducible fashion, and ii) high local drug concentration is avoided since the

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mini-depots are dispersed and distributed over large surfaces, reducing the risk of mucous irritation, Table 2.

An adjustment of the release rate of the depot according to its transit time through the small intestine is essential to the achievement of a satisfactory bioavailability, as the greatest absorption capacity is generally possessed by this part of the gastrointestinal tract, particularly the jejunum and the proximal ileum.

Single-unit preparations tend to follow the food having a normal transit time through the small intestine that varies between 3 and 8 hours (29). Accord-

TABLE 2.

SINGLE-UNIT DOSE	MULTIPLE-UNITS DOSE
Characteristics	
■ Transport dependent on gastric emptying.	■ Transport virtually independent of gastric emptying.
■ Transport strongly influenced by intestinal motility and transit time of food.	■ Transport only moderately affected by intestinal motility and transit time of food.
Varying rate and extent of bioavailability.	Reproducible bioavailability.
Risk of accumulation of doses.	No risk of accumulation of doses and its consequences.
Risk of high local drug concentrations.	
Risk of local irritation.	
■ Tablets non-dividable	■ Tablets dividable

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ingly, 6-10 hours is recommended by many authors as the maximum duration of *in vitro* release from single-unit depots (5,30).

As the sub-units of the multiple-units formulations are distributed freely throughout the gastrointestinal tract, their transport is to a greater extent independent of the transit time of the food. Hence the bioavailability of these products is less subject to variations in both gastric emptying and intestinal transit time (31), providing a more secure interaction between *in vitro* release and bioavailability and thus a more reproducible effect.

Finally, this type of formulation facilitates a better localisation of the depot towards the optimum absorption site as an adjustment of the size and specific gravity of the mini-depots may be used to influence – especially reduce – their transit time (32).

PLASMA CONCENTRATION

Depending on the over-all absorbability of the active agent the plasma concentration/time curve will show a certain degree of intra- and inter-individual variations. Changing from instant release to timed release will usually produce an increase in this variation, because an external factor is added to the physiological factors governing the absorption, distribution, and elimination of the drug (33).

The formulation of the product is essential to the influence on the variance by this new factor. The previous considerations suggest that by far the largest contribution to the variation will be supplied by the single-unit dose. The easy passage through the pylorus and the dispersal in the gastrointestinal tract of the mini-depots from a multiple-units dose suggest a more

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uniform absorption and consequently favours a reproducibility of plasma concentration and effect that is comparable to that of an instant-release dose.

Corroboration of these assumptions, however, is not easily obtained from the literature. In the reported studies, conventional tablets or solutions have been compared with either a single-unit preparation or a multiple-units preparation while a direct comparison between two such preparations having identical *in vitro* release profiles has not yet been reported.

A few drugs as for instance acetylsalicylic acid (ASA) have, however, during the years been formulated according to both the single- and the multiple-units principle, in enteric-coated as well as in true controlled-release formulations. Comparisons between the individual studies performed may allow at least cautious conclusions.

Enteric-Coated ASA

Leonards & Levy (19) compared ASA in a solution with enteric-coated single-unit ASA tablets and found that the reproducibility of the salicylate plasma concentration obtained with the latter was by far the poorest, in particular as regards the time of maximum concentration while the level was generally lower. In commenting on their results the authors mention that as the transport of solid objects from the stomach to the intestine is essentially a random process, the variation would, in all probability, have become even larger if the dose of the enteric-coated preparation had consisted of one tablet instead of three. Green (34), on the other hand, comparing ordinary ASA tablets with tablets of enteric-coated ASA microspherules, i.e. a multiple-units preparation, found plasma concentrations

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varying among and within subjects to the same magnitude for both preparations and which were, moreover, similar to the variations obtained with ASA solutions in the study by Leonards & Levy.

Controlled-Release ASA

Wiik *et al.* (35) compared the plasma concentrations after administration of four types of ASA preparations, Conventional, soluble, and enteric-coated tablets as well as microencapsulated ASA tablets with a release rate of approximately 20-25 % per hour. The authors found the largest variation in plasma concentration for the enteric-coated tablets while the degree of variation for microencapsulated ASA was comparable to that of plain tablets, whereas the soluble tablets produced the least variation.

Altogether these results suggest that a direct comparison between a single-unit and a multiple-units dose with identical *in vitro* release profiles will reveal a variation in plasma concentration that is smallest for the multiple-units dose, but there is an obvious need for actual investigations in order to verify the truth of this theory.

TOXICOLOGICAL ASPECTS

The toxicological importance of incorporating a drug into one of the two described types of controlled-release forms must be judged by experiences from normal therapeutic use as well as from overdosage (4).

In therapeutic use the multiple-units tablet has the great advantage of being dividable without the depot effect being destroyed (10). A flexibility of administration similar to that of instant-release pro-

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ducts is thus provided, and the possibilities of an individually adjusted dosage in long-term treatment are increased. Consequently, the patient may benefit from the advantages of a controlled-release formulation, including a reduced dosage frequency, without being continuously exposed to doses in excess of what is therapeutically required as may be the case with single-unit depots.

Besides dividing, a multiple-units tablet may also be more finely partitioned without the release rate being altered. Thus, patients who traditionally have crushed or chewed their tablets at ingestion may continue to do so without risking an unintended sudden release of a large amount of drug causing a toxic reaction.

Overdosage with controlled-release preparations involves special problems. On one hand the slow release and consequently slow absorption implies a lower acute toxicity, on the other hand the less dramatic appearance of the symptoms may result in an overdosage being recognized too late and thus render more difficult the treatment of poisoning (4,36).

A particular problem of some of these preparations is posed by the larger amount of active ingredient per dose unit, at times corresponding to several doses of unretarded drug which means that fewer dose entities are required for an overdosage. Both by accidental intake, e.g. by children and by intended overdosage (suicide attempts) such products are dangerous, particularly the single-unit type due to the risk of a sudden increase of the release rate caused by a physical influence like chewing (5,6).

Discussions concerning the danger of depot preparations tend, however, to overlook the fact that the pos-

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sibility of preventing a fatal outcome of an overdosage may at times be greater for depot preparations of the multiple-units type than for instant-release preparations. By early recognition of the situation the absorption of some of the ingested drug may be inhibited by gastric lavage, as not only a part of the already released drug but also the mini-depots can be retrieved through the tube (4). Single-unit tablets, on the other hand, cannot be retrieved in this fashion (37).

LOCALLY IRRITATING DRUGS

There is general agreement that to prevent drug related local irritation and/or anaesthesia of mucous membranes, a high local drug concentration must be avoided anywhere in the alimentary canal, be it, Mouth, oesophagus, stomach, or intestine (25,26).

At first attention was mainly paid to stomach irritation, and enteric coating became widely adopted as the solution to this problem. For some drugs, however, this solution ought to be considered obsolete, partly because of the erratic onset of action (19,38) and, partly because of the not so infrequent cases of severe mucous irritation occurring in the small intestine where – due to the instant drug release in this environment – the local drug concentration actually may become very large (39).

In comparison the controlled-release single-unit products, which retain their control of the drug release during the whole passage through the body, do represent a step forward when correctly applied (40,41). But they cannot be considered completely without hazard because their passage like that of the enteric-coated tablets may be delayed unpredictably by trapping in the oesophagus, at the pylorus, or in intestinal folds and

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diverticles where eventually a significant amount of drug may accumulate (42-53).

There is every reason to believe that controlled release according to the multiple-units principle is by far the superior solution. The mini-depots that are released upon disintegration of the capsule or tablet and dispersed solely as a function of time are distributed over an adequately large surface to preclude a high local drug concentration anywhere. Neither do convincing reports exist describing cases of irritation or ulceration of the mucous membranes caused by such preparations, and they are recommended by several authors as a means of preventing this risk (e.g.48,50). Besides, both clinical trials and animal experiments with well-known irritants like potassium chloride and ASA confirm that multiple-units products are tolerated significantly better than single-unit products such as enteric-coated tablets and matrix tablets (54,55).

CONCLUSION

Reproducibility with respect to therapeutic effect as well as the lowest possible risk of side effects are demands that any modern pharmaceutical formulation should fulfil, especially when intended for long-term treatment which applies to most controlled-release preparations.

The present knowledge suggests that the meeting of the demands varies considerably in extent according to whether the single-unit dose principle or the multiple-units dose principle is applied.

Both with respect to reproducibility and low risk of side effects the latter appears preferable. The main reasons for this superiority are, i) that the pas-

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sage of the drug through the alimentary canal has a high degree of independence of the mechanisms determining the rhythm of food transport, in particular opening of the pylorus, and ii) that the drug is rapidly distributed over a large surface which secures optimum utilization of the absorption capacity along with a reduced or eliminated risk of local irritation.

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