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# RECENT DEVELOPMENTS IN DOSAGE FORM DESIGN*

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## ABSTRACT

Recent developments in dosage form design are discussed from the viewpoint that there are three key objectives in formulation; optimum biological availability, minimum side effects and maximum patient compliance. The pilocarpine Ocusert device (Alza) and the talampicillin prodrug (Beechams) are taken as examples of a physical and chemical approach to rational drug delivery.

## INTRODUCTION

Professor A. H. Beckett of Chelsea College, University of London, was one of the first people to emphasize the considerable different between a drug and a formulated medicine. His

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simple but important statement that 'A drug is not given to man; what is given is a preparation containing the drug' has been widely reported. Dr. John Wagner in the United States has said a similar thing; 'The dosage form of a drug is a drug delivery system and almost anything you do to the system may alter the rate and amount delivered to the desired place in the human body (1).

This paper will consider such conversion of a drug into an effective dosage form and will describe two recent developments in dosage design. Firstly it is constructive to consider the various phases of importance in drug administration and drug action. Ariens (2) has delineated three separate phases of drug action following oral administration of a solid dosage form (tablet or capsule).

i) Pharmaceutical Phase: The disintegration of the dosage form and dissolution of the active substance so that the drug is in solution available for absorption (pharmaceutical availability).

ii) Pharmacokinetic Phase: The absorption, distribution, metabolism and excretion of the drug so that the drug is available for action (biological availability).

iii) Pharmacodynamic Phase: Drug-receptor interaction in target tissue leading to some form of pharmacological effect.

I will say a few words about phase (iii) and then concentrate my attention on phase (i).

Phase (ii) has been dealt with in detail by others elsewhere.

## DRUG SYNTHESIS AND DRUG DESIGN

New drugs are discovered by a lengthy process of chemical synthesis and the screening of new compounds for pharmacological activity. This is an expensive procedure the success rate is low. For example Redl and others (3) have stated that to develop a potentially useful therapeutic agent to the point of United States regulatory approval in 1974 typically demanded an investment of some $11.5 million in support of an 8-10 year programme. They predicted that by 1977 the necessary investment was expected to rise to $40 million. As a consequence many workers have attempted to rationalize the process of drug design by means of structure-activity relations, the hope being that one might be able to predict deductively the most suitable compounds to synthesize and test. Two separate approaches to quantitative drug design can be distinguished (3):-

Lead optimization; design of optimally active compounds within a lead series; and

Lead generation; design of optimally active compounds outside a lead series.

The first method is relatively successful, whereas the second is still in its infancy and future progress awaits the development of the theory and application of molecular orbital calculations. By far the most popular and best known lead optimization method is that of Hansch and colleagues (4) where biological response (BR) can be correlated with various physicochemical properties of a drug molecule by means of linear free energy equations.

$$\log Br = a + b + d E_s + \ldots \quad (1)$$

is a hydrophobic substituent parameter derived from partition coefficients,

is the Hammett (or Taft) electronic parameter, and

$E_s$ is a steric parameter.

Such equations have been an important advance in Medicinal Chemistry but as with any new approach based on statistical techniques the Hansch analysis method has been grossly over-exploited and overextended. Hansch and Unger (5) have rightly stressed that it should be recognised that over reliance on statistical criteria to the neglect of common sense is a dangerous and all too frequent abuse. It would be unfortunate indeed if the Hansch method were to fall into disrepute through no fault of its own.

At this juncture I will pose a controversial question: "Do we really need many more 'wonder' drugs or should more

attention be focussed on the problems that concern the effective delivery of existing drugs and medicines?" It is my belief that more attention should be paid to drug dosage design and drug administration and the major part of this paper will be devoted to this theme.

## PROBLEMS OF DRUG ADMINISTRATION

There are three main problems that concern the effective administration of drug substances in formulated medicines.

1. Bioavailability. Is the drug released at the correct time, in the correct place, in the correct quantity?

2. Adverse reactions and side effects. Can they be reduced or even eliminated?

3. Patient compliance. Has the patient taken the medicine according to the prescribed regimen?

The properly designed medicine must take each of these considerations into account, and there are three ways in which this may be achieved; route of administration, pharmaceutical formulation, and chemical modification (reversible derivative formation). These alternatives may be used singly or in combination. Two recent examples of pharmaceutical products that employ a physical and a chemical approach will be described below, but at this stage I wish to consider the route of administration and the importance of preformulation studies.

## ROUTE OF ADMINISTRATION - ON TARGET THERAPY

A biological means of improving biological availability reducing adverse reactions and improving patient compliance is to alter the route of administration. For example, absolute biological availability can be achieved by an intravenous injection, while the complexities of oral administration (e.g. food, physiological factors, first pass phenomenon) can be avoided to a considerable extent by rectal administration. In addition much has been written lately about 'on-target' therapy and the recent withdrawal of certain brands of oral contraceptives is a timely reminder of some of the disadvantages of present-day drug therapy. The oral administration of potent drugs such as oral contraceptives to have action at a localized specific site is an outdated concept. The body is swamped by the drug and only a very small quantity reaches the site of action. In order to achieve the desired pharmacological effect much larger doses than really necessary have to be used and as a consequence adverse side effects may result. A shot-gun to kill an ant' to say the very least. An alternative and much more sophisticated approach is to get the drug much closer to the site of action. In the field of contraception this has been achieved by means of a polymeric intrauterine device containing progesterone that releases the drug at a constant rate of 65 g/day for one year

(6). The total amount of drug administered is vastly reduced and patient compliance is improved.

## PREFORMULATION STUDIES

Before turning attention to physical and chemical approaches it is instructive to consider the importance of preformulation studies.

The possible disadvantages or problems manifested by a drug substance can be listed as a) poor absorption, b) poor stability (in vitro or in vivo), c) taste, d) smell, e) irritation (gastrointestinal tract) pain (injection) and f) slow or rapid metabolism. It will be during preformulation studies that many of these disadvantages became apparent. As an example we will consider poor oral absorption and how it may be overcome.

Potential absorption problems may occur due to low aqueous solubility (dissolution rate) of the drug; a high degree of dissociation of the drug over the physiological range of pH; and a low oil-water partition coefficient.

Fortunately it is often possible to predict likely problems or the absence of them, in preformulation work. For example if the drug has a solubility greater than 1% at 37°C over the pH range 1 to 7 then there are usually no absorption problems resulting from solubility (or dissolution) characteristics. In

the event of dissolution rate limited absorption, the pharmaceutical availability of a drug can be increased by a variety of techniques that include; reduction of drug particle size (increased surface area); use of the salt form of an acidic or basic drug; solid solutions; solubilization; chemical modification etc.

The prediction of potential absorption problems due to poor permeability of a drug through biological membranes is rather more difficult. Purely physicochemical data such as the oil-water partition coefficient are limited in their predictive ability and it is usual to employ some form of experimental determination using a 'model' system. Kaplan (7) has suggested the use of a segment of intestinal mucosa in vitro. The drug is placed within a sac of the material and the lag time and amount of transferred per unit time are measured (figure 1). These data can be indicative of permeability limited absorption problems. For example lag-times greater than 60 minutes can be associated with poor absorption in vivo. Reduced biological availability due to poor permeability can be overcome by chemical modification (analogues). For instance the hydrophobic character of a drug molecule can be enhanced by decreasing the number of polar groups or increasing the number of non-polar groups. Alternatively a reversible drug derivative can

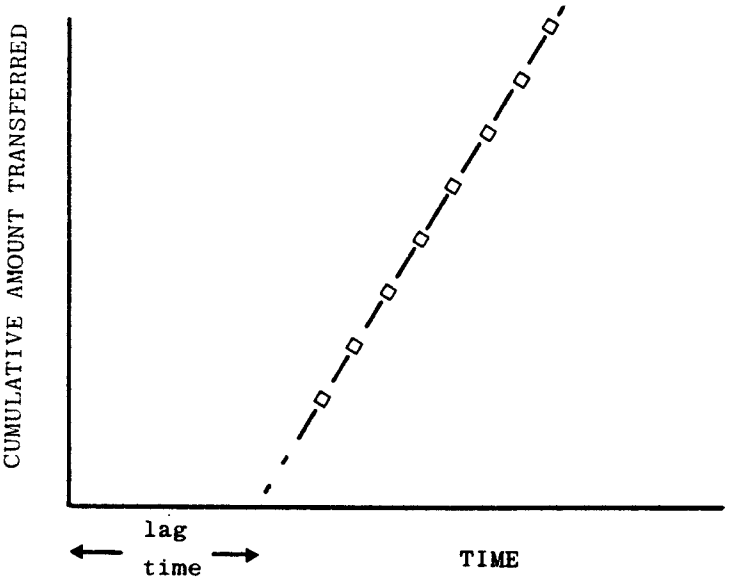



FIG. 1

IN VITRO ASSESSMENT OF DRUG PERMEABILITY

be made (Prodrug). This approach will be discussed in greater detail below. Theoretically it is also possible to enhance permeability by increasing the diffusivity of the molecule by reducing its size, however in practice this is an ineffective process. To see why we can compare the partition coefficient (hydrophobicity) of a substance with the molecular weight (related to diffusion coefficient); a seven fold change in molecular weight can result in a sixty million fold change in partition coefficient!

While dissolution and permeability are essential factors that can influence biological activity it should always be remembered that a low blood level after oral administration as compared with the IV situation may be a consequence of degradation of the drug in the gastrointestinal tract or metabolism of the drug in the liver (first pass effect).

## A PHYSICAL APPROACH TO DRUG DELIVERY

There can be no one in the field of drug dosage development who has not heard of the Alza Corporation of California and their activities in the field of drug polymer devices. This company is presently working on drug delivery systems for the eye (Ocusert), uterus (Progestasert), skin (transdermal therapeutic systems - TTS) and oral route (Oros). It is their Ocusert device containing pilocarpine for the treatment of glaucoma that I wish to use as an example of a physical approach to drug delivery.

Turning attention firstly to patient compliance, Spaeth (8) has shown that some 30% to 60% of patients fail to take pilocarpine eyedrops as directed. The instillation of pilocarpine eyedrops to reduce intraocular pressure can create visual disturbances (miosis and myopia), discomfort and sometimes disability which may be sufficient to disrupt adherence to a

given regimen. In order to overcome those problems a polymer (ethylene vinyl acetate copolymer) drug device has been developed by Alza. This provides a zero order release of of pilocarpine at a predetermined rate (20 g or 40 g per hour) for 7 days. Such a zero order process will provide for steady state drug levels in the tissues of the eye. Furthermore, release of the drug from the device is a diffusion controlled process and release rate (diffusional flux) can be related to the important physicochemical variables in the usual way (Fick's Law) (9).

$$\text{Release rate} = \frac{DA \quad C}{h} \qquad (2)$$

where D is the diffusion coefficient, A is the membrane area, C the difference in drug concentration inside and outside the device (relatable to drug solubility and partition coefficient) and h is the membrane thickness.

A comparison of the total amount of drug delivered and number of applications for the Ocusert and the conventional eyedrop system are given in table 1. Not only is there a vast improvement in patient compliance but also side-effects are almost eliminated (on initial insertion of the Ocusert some side-effects will result, however, the weekly procedure can be conducted last thing at night). A comparison of the induced myopia

TABLE 1

CONTRASTS BETWEEN OCUSERT SYSTEM AND EYEDROP THERAPY

| | Eyedrops 2% q.i.d. | Ocusert 20 g/hr | Ocusert 40 g/hr |
|---|---|---|---|
| Amount of pilocarpine delivered (7 days) mg | 28 | 3.4 | 6.7 |
| Number of applications | 28 | 1 | 1 |

effects are given in figure 2 for two eyedrop and two Ocusert formulations. The difference is most impressive.

## A CHEMICAL APPROACH TO DRUG DELIVERY

The prodrug reversible drug derivative concept has been mentioned above. The drug is modified chemically to produce a new compound that has improved characteristics (e.g. better absorption) but once absorbed it breaks down rapidly to form the original compound. An excellent review on reversible drug derivatives has been given by Sinkula and Yalkowsky (10). Derivatives may be formed, not only to modify absorption or resorption but also to alter drug transport to site specific tissues, to change duration of activity or to modify irritation, taste or odour.

In the United Kingdom a prodrug form of ampicillin (talampicillin) has been marketed recently (11) and this will

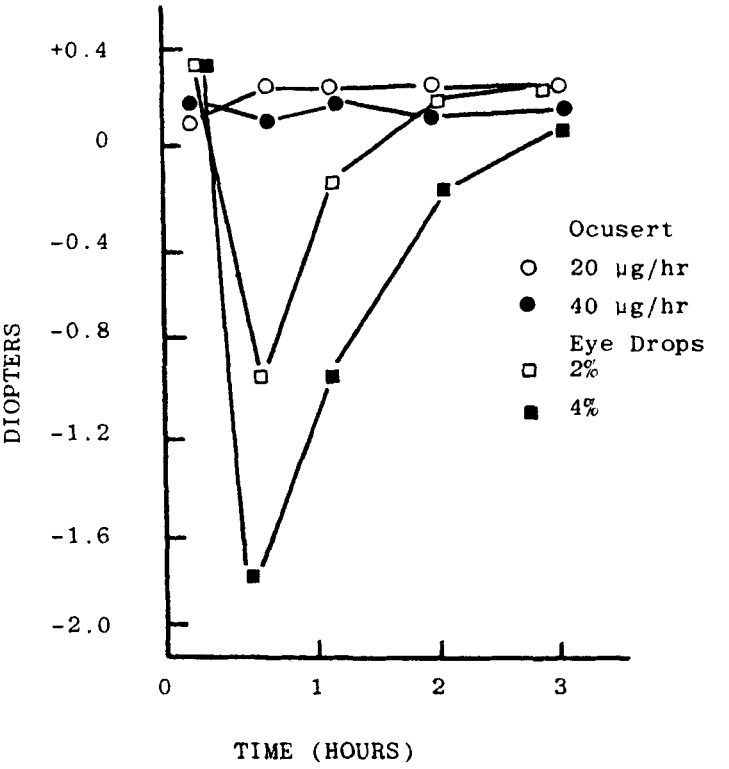
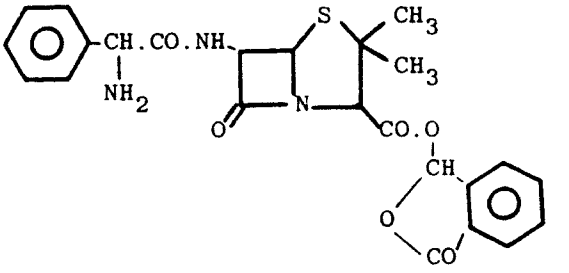



FIG. 2

PILOCARPINE INDUCED MYOPIA, REFRACTIVE CHANGES IN NORMAL VOLUNTEERS

serve well as our example of a chemical approach to drug delivery. Talampicillin is the phthalidyl ester of ampicillin. This ester form is more lipophilic than ampicillin and consequently is better absorbed in the gastrointestinal tract. It is hydrolysed to ampicillin by tissue esterases in the gut mucosa. The improved absorption gives an improved biological availability (figure 3).

TALAMPICILLIN



AMPICILLIN

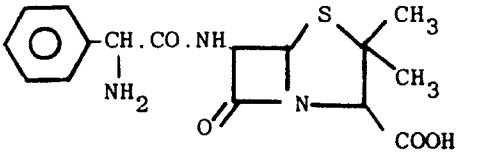


FIG. 3

STRUCTURES OF TALAMPICILLIN AND AMPICILLIN

A higher peak ampicillin level is reached at an earlier time than with ampicillin. Moreover 70% of the dose is absorbed and excreted as ampicillin and its metabolite, penicilloic acid. This may be contrasted with ampicillin itself where only about 40% of the administered dose is absorbed. Also of interest is the fact that the absorption of talampicillin is unaffected by food so that it may be taken with food. Ampicillin should be taken 1/2 to 1 hour before food.

Side effects in the form of diarrhoea were significantly reduced (table 2) since talampicillin itself has no intrinsic antibacterial activity and thus does not affect the gastrointestinal microflora (12).

The data shown in table 2 also demonstrate that the dosage regimen for talampicillin is different from that for unmodified ampicillin. The three times a day dosage with talampicillin is more convenient than the four times a day regimen with ampicillin. Coupled with the fact that talampicillin can be taken with food, improved patient compliance is to be expected. The total amount of drug (ampicillin) administered is also reduced. The t. i. d. regimen for talampicillin gives 750 mg of derivative daily, which is equivalent to 507 mg of ampicillin daily (compare with 1 g daily for the unmodified drug).

TABLE 2

CONTRASTS BETWEEN TALAMPICILLIN AND AMPICILLIN

| | AMPICILLIN | TALAMPICILLIN |
|---|---|---|
| Dose Regimen | 250 mg q. i. d. | 250 mg t. i. d. |
| No. of Patients in trial | 405 | 394 |
| No. of Patients reporting diarrhoea as side effect | 35 (8.6%) | 17 (4.3%) |

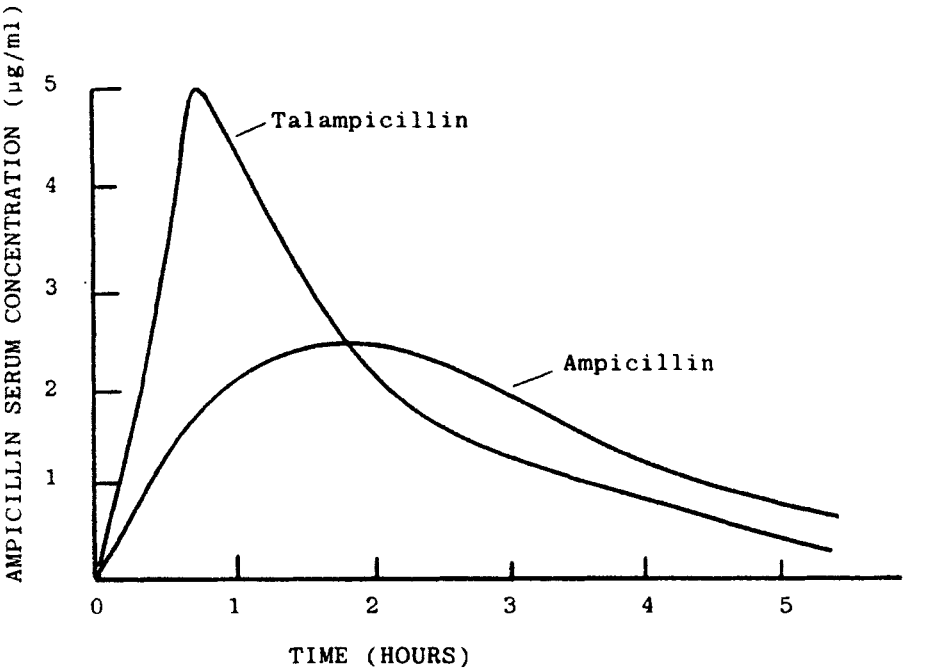



FIG. 4

COMPARATIVE BIOLOGICAL AVAILABILITY OF TALAMPICILLIN AND AMPICILLIN (FROM MANUFACTURERS DATA)

## SUMMARY AND CONCLUSIONS

The pharmaceutical scientist of today can use a variety of approaches for the rational design of drug delivery systems. He may choose a biological, physical or chemical attack or some suitable combination of each. His aims are threefold; to provide the required optimum biological availability of the drug

with a minimum of adverse reactions and side effects and to ensure that the patient takes the drug according to the correct regimen.

Table 4 summarizes and contrasts two examples of a physical and a chemical approach to drug delivery.

TABLE 4

PHYSICAL AND CHEMICAL APPROACHES TO DRUG DELIVERY

| Requirements | Physical Approach | Chemical Approach |
|---|---|---|
| | Pilocarpine-Polymer Combination (Alza) | Talampicillin Prodrug (Beechams) |
| Improved Bioavailability | Zero order release of pilocarpine (40, or 20 g/hour) provides a steady state level of the drug in ocular tissues. It maintains higher drug levels in the aqueous humour than eyedrops. | 250 mg talampicillin tablet (equivalent to 169 mg ampicillin) produces a peak serum level of ampicillin at least twice as high as that achieved for a 250 mg ampicillin capsule. |
| Reduction of side effects | Reduced incidence of visual disturbances (myopia, miosis) as compared with eyedrops. | Reduced incidence of diarrhoea as compared with unmodified ampicillin. |
| Improved patient compliance | One device inserted once a week instead of drops every 6 hours. | T. i. d. dosage, with food instead of q. i. d. 1/2 or 1 hour before food. |

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