DELIVERY SYSTEMS FOR PATIENT COMPLIANCE

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1. INTRODUCTION

Not long ago, somebody told me that drugs are made because the drug industry wants to live; the physician prescribes the drug because he wants to live, and the patient doesn't take the drug because he wants to live too. Now, let's talk seriously about this topic !

Today the prescribing physician has many highly potent drugs at his disposal. The main interest of the physician is the therapeutic effect. The therapeutic success depends to a large extent on the question of whether or not the patient is prepared to follow his physician's instructions. This is called patient compliance. Patient compliance cannot be taken for granted. From market surveys it is known that some 35 to 45 % of all prescribed drugs are not taken. As a consequence of this the therapeutic goal of the doctor is not achieved in a large proportion of the patients. Thus, the National Health Services suffer also from this fact because they have to pay the bill. It is clear that this problem is of special importance in long term therapy, as for the treatment of hypertension or psychiatric disorders etc.

This presentation will investigate the problem with respect to the most commonly used delivery systems, the solid dosage forms. What can we do to ensure optimal patient compliance ? What do we mean when we talk about patient compliance in connection with a drug ? Do we mean that the acceptability of the drug is good, that it is presented in a pleasant form and attractively packed ? Or is patient compliance something which comes as a desirable side effect of the drug's active ingredient ?

Maybe it is interesting to recall, however, that at the time of Galen, and even much later, patients were given almost every kind of organic

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and inorganic substance — crocodile dung, swine's teeth, donkey's hooves, fly excreta, powdered gemstones or bricks, and so on. Despite this horrifying and to us, almost unbelievable treatment, we cannot deny that the physicians of the past must also have been successful healers. Today we know that their effectiveness was the result of a placebo effect, that is to say of suggestion, under optimum conditions, deriving from a very intensive interaction between physician and patients. Nowadays, in certain cases, treatment is hindered by the lack of a sufficiently harmless placebo — and of a doctor with time to spare for his patients as well as an adequate degree of charisma. What conclusion can we draw from the experience of the ancient physicians and our present situation ?

2. EXTERNAL FACTORS FAVOURING PATIENT COMPLIANCE IN A DRUG DELIVERY SYSTEM

1. Firstly, we should not simply ignore the placebo effect but actively foster it, side by side with the drug's natural effectiveness.
2. Secondly, we should try to find more ways of improving communication between the doctor, the pharmacist and the patient.

As regards the first of these aims, we can say that it is ethically sound and not to be construed simply as a salesman's trick. The presence on the market of tablets put up in striking colours — bright scarlet, malevolent green, diabolical yellow, restful blue — is not without a thought for the therapeutic effect of their appearance alone. As the number of internationally permitted dyes is reduced, however, it is becoming increasingly difficult to make use of the suggestive effect of symbolically and psychologically meaningful colours in the healing process. Apart from shape and colour, the taste of a drug also makes its contribution to patient compliance. Thus effectiveness in a drug is today not necessarily equated with bitterness. This is of particular importance where paediatric preparations are concerned, for it can make things easier for a sick child's mother or nurse.

Among the many factors affecting patient compliance we should not overlook the nature of the package. Thus the blister packs now considered the last word in packaging are not exactly the best thing for people with rheumatic hands.

Dosage regimen is also a decisive factor. This was demonstrated by a study done with an antidepressant : Four times a day dosage led to

a patient compliance of only 30 %. The corresponding once a day dosage led to a three times higher patient compliance !

Let me summarize some of the most important external factors influencing patient compliance :

— Insufficient influence of the doctor on the patient;
— Lack of awareness of the illness by the patient;
— Unclear or confusing text of package inserts;
— Discomfort of usage of the drug or even of a large number of drugs;
— Dosage regimen.

3. INTRINSIC FACTORS OF A DRUG TO ENCOURAGE PATIENT COMPLIANCE

Since a drug manufacturer is hardly in a position to have much say in the personal relationships between doctor, pharmacist and patient, it is important for us to develop dosage forms that are, so to speak, convincing in themselves as well as easy to take. When I say convincing, I have in mind the following properties as pre-requisites for « intrinsic » compliance :

1. A well-established profile of activity, or patient's experience of its effectiveness.
2. Well tolerated, that is to say few, if any side effects.
3. Absence of ingestion problems, with doses to be taken at reasonable intervals such as once a day.
4. If necessary, a combination with other indicated active substances.

These requirements take into account the fact that important properties specific to the active substance may also play an important or even decisive role in patient compliance. The solution for these problems can often only be found at the bench.

4. OPTIMIZATION OF A DRUG IN RESPECT OF PATIENT COMPLIANCE

On the subject of « From Bench to Bedside », I propose now to go rather more deeply into the problem of developing solid dosage forms with a view to optimizing patient compliance. In addition to its may be less important shape, colour and wrapping, such a drug should display the following « inner » qualities (as in the choice of a spouse,

we should look for the inner as well as the obvious qualities !) :

1. Optimum bioavailability.
2. Depending on its nature (action, side effects), the active substance should be released either rapidly or at a specially adjusted rate.
3. Reasonable technical characteristics such as, in tablets, hardness and good abrasion resistance.

Since for obvious reasons we cannot test every batch of a drug for bioavailability and effectiveness, optimization must be achieved by testing substitute parameters like tablet hardness and disintegration time. The most important of such substitute parameters is, however, the in vitro rate of release of the active substance. Appropriate biopharmaceutical tests will enable the corresponding requirements to be formulated. If rapid onset of action is called for, rapid release of the active substance followed by its rapid absorption must be aimed at. If too rapid a dispersal of the active substance in the blood stream causes undesirable side effects, however, the release rate must be suitably regulated. In addition to this biopharmaceutically relevant question of active substance release, tablets must possess adequate hardness and abrasion resistance. Improvement of one parameter often goes hand in hand with deterioration of another, so that the art of optimization is no easy task. Nowadays the pharmaceutical chemist is helped in this strategy by modern mathemathical techniques (1, 2). Let me now outline the strategy to be adopted for such an optimization process, namely in respect of the following characteristics :

1. Dissolution rate.
2. Disintegration time.
3. Tablet hardness.
4. Friability.

Optimization of our solid dosage form will involve varying the following factors :

1. The filler (lactose, dicalcium phosphate).
2. The disintegrating agent.
3. The lubricating agent.
4. The binding agent.
5. The tabletting pressure.

If we use the trial plan devised by Box and Wilson, we shall need to prepare 27 different batches (Table 1).

Table 1. — *Orthogonal trial plan (Box and Wilson) with* $\alpha = 1.547$. *The units of the factors* x_i *are coded* (1).

Tablet formulation No.	Factors				
	x_1	x_2	x_3	x_4	x_5
1	−1	−1	−1	−1	+1
2	+1	−1	−1	−1	−1
3	−1	+1	−1	−1	−1
4	+1	+1	−1	−1	+1
5	−1	−1	+1	−1	−1
6	+1	−1	+1	−1	+1
7	−1	+1	+1	−1	+1
8	+1	+1	+1	−1	−1
9	−1	−1	−1	+1	−1
10	+1	−1	−1	+1	+1
11	−1	+1	−1	+1	+1
12	+1	+1	−1	+1	−1
13	−1	−1	+1	+1	+1
14	+1	−1	+1	+1	−1
15	−1	+1	+1	+1	−1
16	+1	+1	+1	+1	+1
17	$-\alpha$	0	0	0	0
18	$+\alpha$	0	0	0	0
19	0	$-\alpha$	0	0	0
20	0	$+\alpha$	0	0	0
21	0	0	$-\alpha$	0	0
22	0	0	$+\alpha$	0	0
23	0	0	0	$-\alpha$	0
24	0	0	0	$+\alpha$	0
25	0	0	0	0	$-\alpha$
26	0	0	0	0	$+\alpha$
27	0	0	0	0	0

After production of the batches, they are individually tested, with the result that we have batch-dependent values for each characteristic tested.

Using these values we can derive a quadratic equation for dependence of each characteristic on the five factors. Table 2 shows the

Table 2. — *Comparison between experimental and calculated values for tablet hardness* (1).

Tablet formulation No.	Calculated value N	Experimental value N	Difference (residuum) N
1	22.62	22.90	0.28
2	26.84	26.70	—0.16
3	59.84	59.60	—0.24
4	40.10	40.20	0.10
5	29.71	30.00	0.29
6	28.87	29.50	0.63
7	35.67	36.20	0.53
8	63.32	63.40	0.08
9	33.48	32.80	—0.69
10	26.74	26.40	—0.34
11	47.64	47.20	—0.44
12	78.58	77.60	—0.98
13	29.81	29.90	0.09
14	30.16	29.80	—0.36
15	67.36	66.90	—0.47
16	49.62	49.50	—0.12
17	45.17	45.40	0.23
18	48.67	49.10	0.43
19	13.52	13.40	—0.08
20	54.88	55.60	0.72
21	41.37	42.70	1.33
22	41.11	40.50	—0.61
23	41.18	40.00	—1.18
24	52.09	54.00	1.91
25	62.60	64.00	1.40
26	41.67	41.00	—0.67
27	46.36	44.50	—1.86

excellent agreement found between the hardness figures from the mathematical model and the measured values. Good agreement was also found in respect of the disintegration time characteristic.

In addition to this numerical comparison, the computer can furnish us with graphs showing the individual dependences.

In the case of the so-called composite plots (Fig. 1), each factor is varied separately, as in the classical method of trial planning. Here we clearly see the positive effect of tabletting pressure on the hardness and the negative effect of the hydrophobic magnesium stearate on the same characteristic. The results can also be illustrated either cartographically (Fig. 2a) or in three-dimensional perspective (Fig. 2b). This latter, which we call a « landscape » picture of the tablet characteristics, may seem rather far-fetched but it has nevertheless one very important advantage: it shows us whether our formulation is to be found in the uncritical region of the plateau or in that of a dangerously steep slope (Fig. 2b).

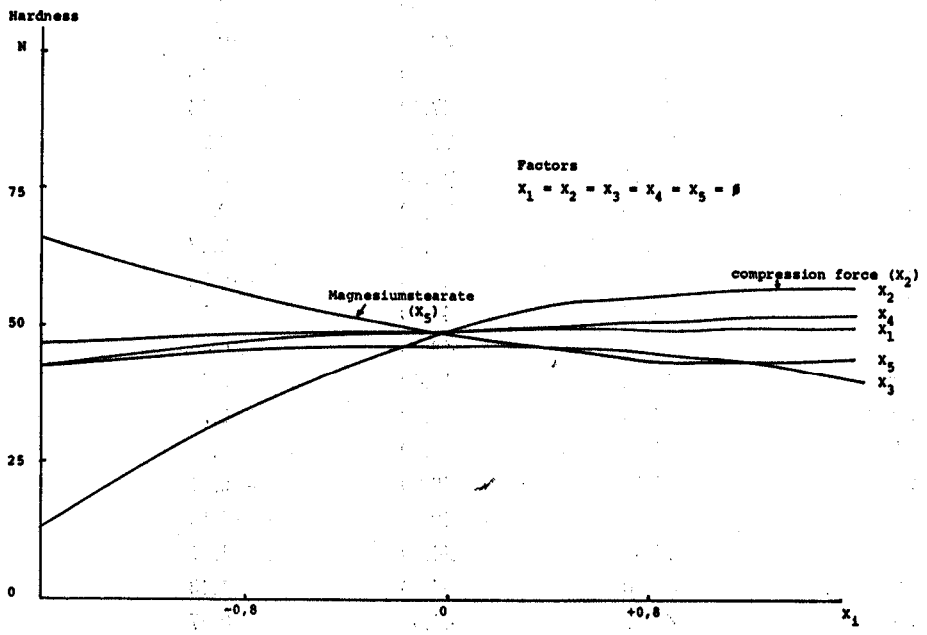

Fig. 1. — Hardness of a Tablet as a function of X_i

In the latter case, even a small change in one excipient — either in processing or quality — can have a very marked effect on a characteristic, so we obviously prefer to stay in the uncritical region.

With due regard paid to the biopharmaceutical requirements, we can now decide on the requirements in respect of the quality characteristics. Since more than one of these criteria must be fulfilled

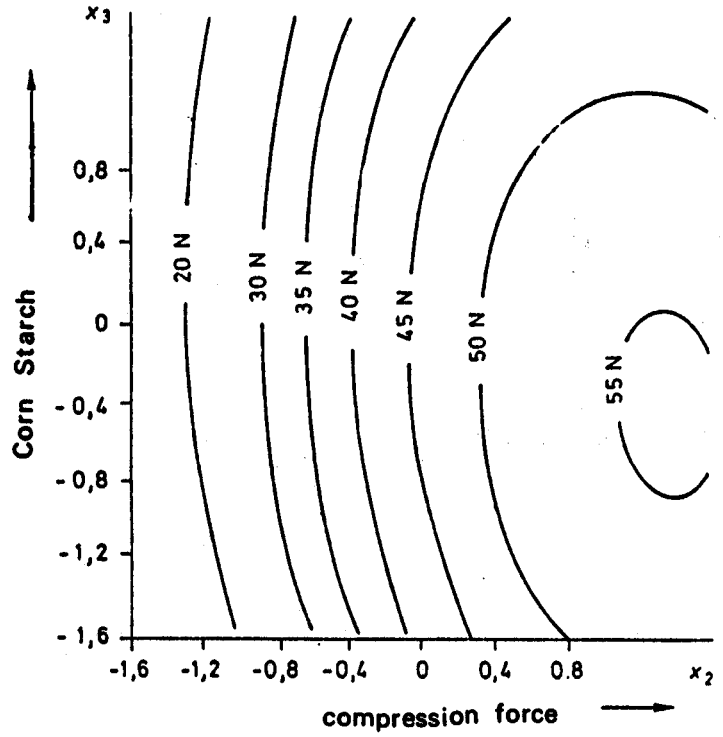

Fig. 2a. — Hardness of a Tablet as a function of compression force and concentration of corn starch.

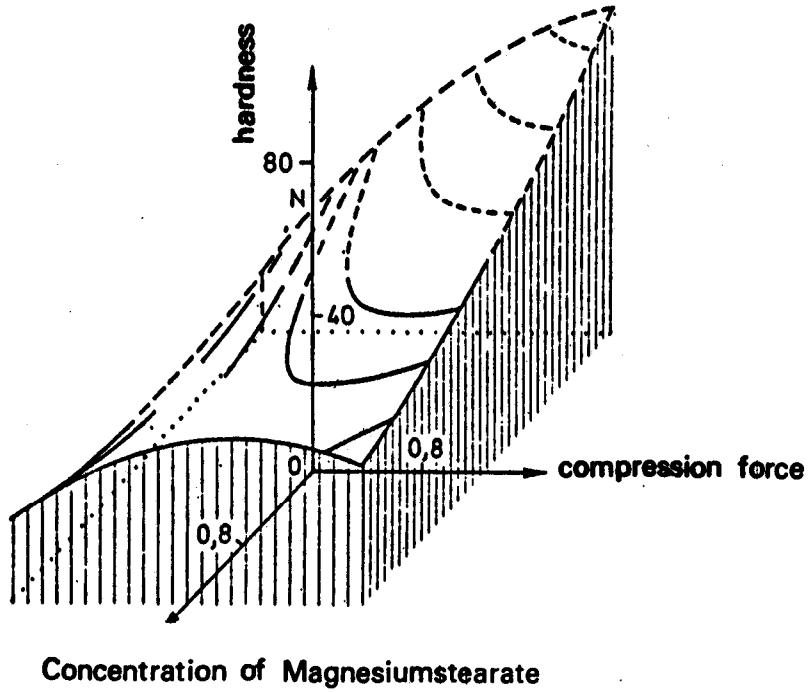

Fig. 2b. — Hardness as a function of compression force and concentration of magnesium stearate.

simultaneously, we use a computer to define the area of the possible formulations. Such an area is shown in simplified fashion in Figure 2c for the characteristics of tablet hardness and friability.

Let me summarize — parallel to the progress in science and better knowledge about its effect and side effects, patient compliance has become more than a packaging problem. Thus, the time, strategy and effort required to get from bench to bedside have changed considerably. Today modern methods such as mathematical modelling are at the disposal of the industrial pharmacist helping to develop better formulations.

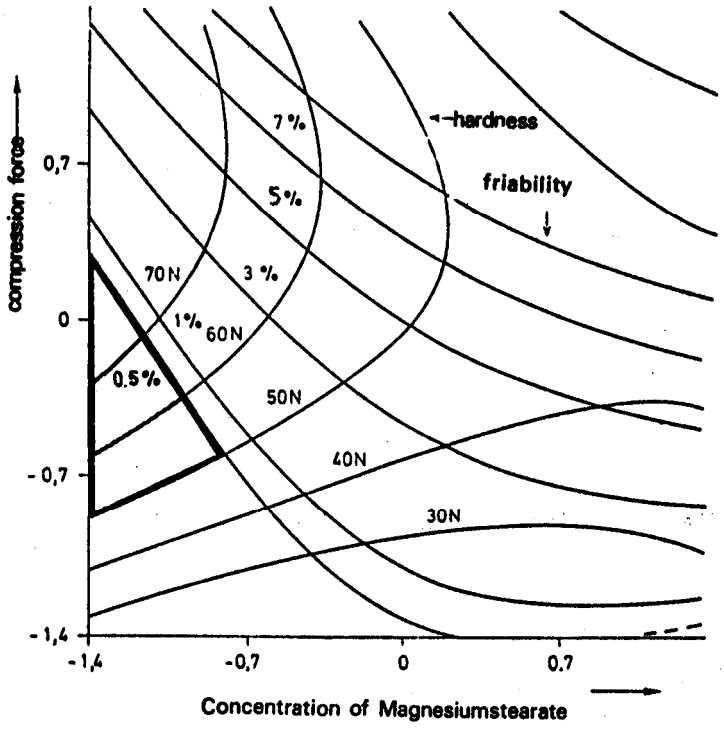

Fig. 2c. — Range of possible formulations, which fulfil the quality requirements (1).

5. CRITERIA FOR OBJECTIVE TESTING OF A DRUG AFTER OPTIMIZATION

Permit me now to take a step away from the bench in the direction of the bedside. It is after all at the bedside that the drug must prove its worth. When a preparation has been finally optimized it is important that we are able to evaluate it objectively before going to registration. As an example let us take the evaluation of a once-a-day dosage form which was developed to encourage patient compliance. Depending on the biopharmaceutical and pharmacokinetic properties of the active substance a once-a-day dosage form is synonymous with a retard form. To adequately judge the effectiveness of a retard form, special criteria were established (3). In order to quantify the retard effect, the maximal plasma level, their half-value height and the half-value duration are determined individually for the retard and non-retard dosage form. (Fig. 3). Thus, two different ratios can be distinguished : the quotient R

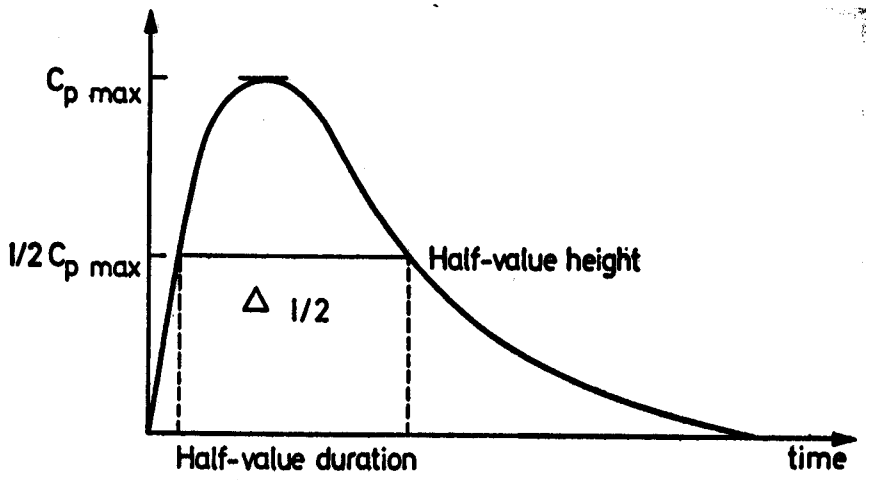

Fig. 3. — Definition of half-value duration and half-value height.

gives the factor by which the half-value duration is extended in the retard formulation compared to a normal form. The value for a good retard form should well differ from unity. The quotient R_o shows the factor by which the peak-heights of the maximal or half-maximal plasma concentrations differ between retard and normal formulation. To achieve adequate bioavailability in the retard form as well as sufficient therapeutic effect the ratio of the plasma half-values should be roughly unity (Fig 4 - Fig. 5) (4).

This is a requirement to which due attention is often not paid, the retard form being developed simply on the basis of differing half-value durations and at the expense of bioavailability. Retard forms with low bioavailability and high normal dosage can present a certain risk when the limits of therapeutic effectiveness are narrow. On the one hand the therapeutically necessary blood level is not reached, while on the other a (possibly individual) over-rapid release of the active substance may result in absorption of the whole nominal dose.

In this connection it is difficult to understand how some workers can see proof of retard action in low bioavailability compared with the normal form. I quote from a published paper (3) on the retard action of a vincamine preparation : « In 12 hours about 70 μg of the drug, corresponding to ca. 1 ‰ of the dose applied, was excreted (in the urine). Since the excretion values for the non-retard form are some 10

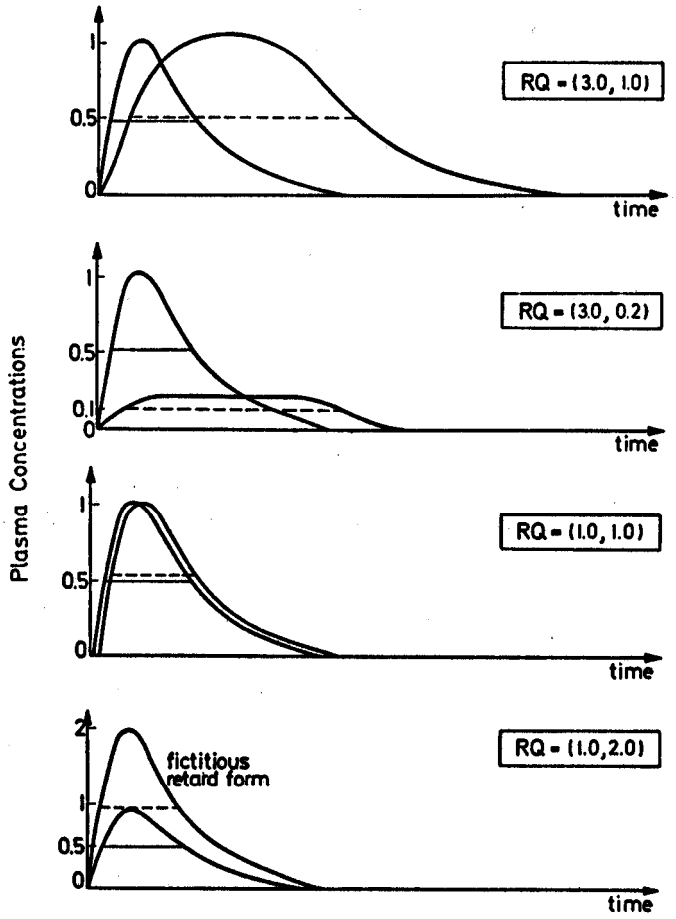

Fig. 4. — Model examples of retard quotients : $RQ = (R_{\Delta}, R_{C})$

$$R_\Delta = 3.6 \pm 0.1$$
$$R_c = 1.0 \pm 0.1$$

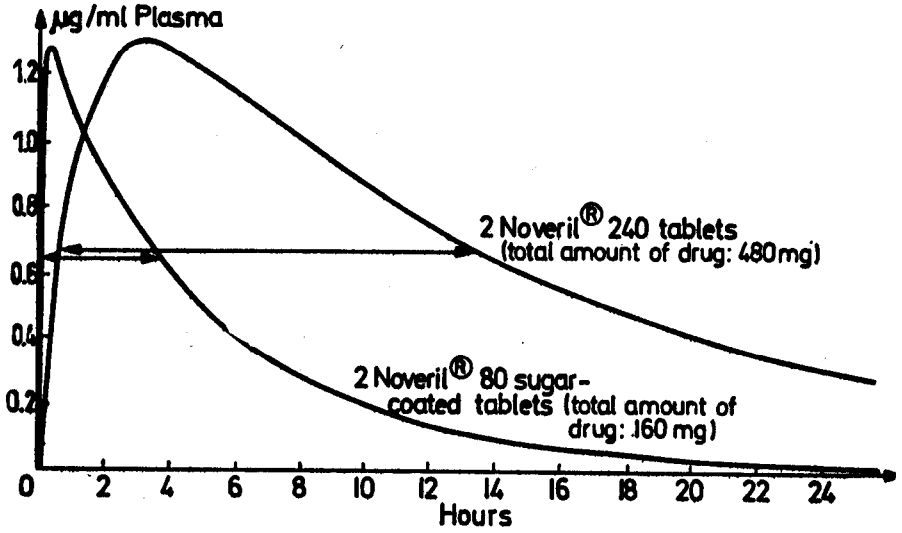

Fig. 5. — Plasma concentrations of dibenzepin hydrochloride in man simulated with the averaged pharmacokinetic constants of Noveril ® and Noveril ® 240.

times greater, this finding also demonstrates the delayed release of active substance from the multi-layer drágées. »

The low bioavailability figure of 10 % of that of the normal form is thus put forward as evidence of the delayed release of the active substance.

Fortunately, there are also papers in which our strict criteria for evaluating dosage forms have been adopted. Thus Morrison *et al.* (5) used these to compare the plasma level curves of enteric and non-enteric coated prednisolone tablets.

I hope that during this short paper I have been able to throw some light on the problem of optimizing drug delivery systems. Perhaps also you will have acquired some idea of the high outlay involved in the business of developing pharmaceutical preparations — and an insight into the very strict criteria applied to the evaluation of these preparations during their development in the company's laboratories.

Although the effort to achieve optimal dosage forms with respect to patient's compliance is high, it is hoped that two goals are fulfilled at the same time:

1. A more effective therapy by a strict adherence of the patient to the prescribed drug and last but not least,
2. a cheaper treatment, as fewer drugs will be thrown away.

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ABSTRACT

Throughout the existence of pharmacy, patient compliance in taking medicine was considered important for a quick recovery from sickness. However, parallel to the progress in science and better knowledge about the fate of a drug once absorbed, its effect and side effects, patient compliance has become more than a packaging or marketing problem. Thus, the time, strategy and effort required to get from bench to bedside have changed considerably. To-day modern methods such as mathematical modelling are at the disposal of the pharmacist to help develop better formulations.

Besides discussing these new tools, an example of special criteria developed to judge the performance of retard formulations is briefly described.

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