Scientific Basis of Clinical Practice

Scientific Principles in Design of Drug Dosage Formulations

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The discovery and development of a new drug can be a lengthy and expensive business (Fig. 1). The starting point is the active compound as synthesized by the medicinal chemist and screened by the pharmacologist. There then follows a series of complex tests and evaluations to produce a satisfactory formulation and sufficient data for presentation to regulatory authorities such as the Committee on the Safety of Drugs. Unfortunately, this aspect of drug research has been sadly neglected until recent years. Today, however, the formulation of new drugs is based on sound physical and chemical principles.

To illustrate some of the concepts involved I will concentrate on the oral route of administration and pay particular attention to the fate of tablets and capsules after administration (Fig. 2). In formulation we can affect the absorption of the drug in two ways: (1) the rate at which the drug goes into solution (dissolution), or (2) the rate of absorption of the drug across biological membranes.

Dissolution of Solid Dosage Forms

Thirty years or so ago the drug industry was almost totally unaware of the question of biological (physiological) availability. The formulator was satisfied with a simple chemical assay plus a few additional tests, as an adequate form of quality

FIG. 2—Fate of a tablet or capsule after oral administration.

control. In 1939 Berry examined tablet disintegration and suggested that it might be an important factor in availability.¹ The fact that the formulation contained the correct quantity of active ingredient was no guarantee of efficacy. Subsequently a disintegration test was introduced into the *British Pharmacopoeia*. This test has been an extremely useful indication of tablet properties but tells one almost nothing about the availability of the drug *in solution*. Thus one can easily formulate a product that will break up rapidly into its original granules and pass the B.P. test but will give an extremely slow release of the drug. (Table I).

Drug availability can be controlled largely by pharmaceutical factors which the formulator can alter.

The rate of dissolution (usually the most important process affecting availability) can be defined by a simple equation:³

$$\frac{dW}{dt} = K S (C_s - C)$$

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FIG. 1—Flow chart development of new drug dosage form.

TABLE I—Disintegration, Dissolution and Availability of Aspirin from Tablets^a

Product	Mean Disintegration time (U.S.P. method) (sec)	Mean Quantity Dissolved in 10 min (mg)	Salicylate Excreted in urine (0-1 hour after Administration of two 300 mg Tablets) (mg)
Study I {1 2 3}	256 <10 <10	242 165 127	24.3 18.1 15.9
Study II {4 5 3}	35 13 <10	205 158 127	18.5 13.6 12.1

where dW/dt is the dissolution rate, S the surface area of the dissolving solid, C the concentration of the drug in the dissolution medium, C_s the concentration of the drug in the diffusion layer surrounding the solid material (saturated solution), and K the dissolution rate constant. Further it has been shown that $K=D/L$, where D is the diffusion coefficient and L is the thickness of the diffusion layer around the solid material. This equation provides us with a rational approach to formulation. We can alter the variables in the equation to retard release (for example, when sustained release is required) or to increase its rate to give maximum effect in the shortest possible time.

The more interesting factors affecting dissolution rate (Table II) will be discussed below.

TABLE II—Factors Which may Change Dissolution Rate

Surface area (S): particle size.
 Saturation solubility of the Drug (C_s): temperature; pH; salt form; particle size; solvation; amorphous state; crystal form; complexation; surface active agents (wetting).
 Diffusion coefficient (D): temperature; viscosity; molecular weight and shape.
 Thickness of the diffusion layer (L): agitation; flow rate.
 Other considerations in manufacturing: physical modification (enteric coating, sustained release); diluents, fillers, binders, disintegrants; granule size, granulation method; surface-active agents; compression force in tableting; tablet hardness, etc.

SURFACE AREAS (S)

A reduction in particle size will increase surface area, often giving an increased availability. Examples are sulphadiazine, nitrofurantoin, aspirin, and griseofulvin. The last is a striking example, for the amount absorbed increases linearly with the logarithm of the specific surface area (Fig. 3). Hence, the dosage of the active principle can be reduced without losing efficacy, simply by reducing the particle size.

FIG. 3—Effect of surface area (Particle Size) on absorption of griseofulvin.

A reduction in particle size is not successful in increasing availability in all cases. The dissolution rate may be too rapid and the drug is available in the wrong part of the gastrointestinal tract. Or rapid dissolution followed by slow absorption may result in the loss of available drug owing to degradation. In addition, powders of very small particle size may be more difficult to wet than the larger sized material, and thus they will dissolve more slowly.

SATURATION SOLUBILITY (C_s)

Saturation solubility may be altered by chemical modification of the drug or by modifying the dissolution environment. Many drugs

currently available are weak acids or weak bases. Their total solubility can be altered by adjusting the pH. For example, a weak base will be freely soluble at the low pH of stomach contents, whereas a weak acid will be poorly soluble. To increase the availability of a weak acid in the stomach we must attempt to raise the pH in the immediate environment surrounding the dissolving solid. This will affect C_s and thus the dissolution rate. Two methods are available. Firstly, we can buffer the tablet by adding a solid basic substance to the tablet formulation. A well known example is buffered aspirin (Table III). Alternatively, and more commonly, we can administer the drug as its sodium salt. Sodium salts of weak

TABLE III—Effect of Buffering on the Dissolution and Availability of Aspirin^a

Dosage Form	Dissolution Rate in vitro —Quantity of Aspirin in Solution in 10 minutes (mg)	Salicylate Excreted in Urine after 1 hour (mg)
Unbuffered tablets*	275	13.5
Buffered tablets	411	17.2
Aspirin solution	—	22.3

* Mean value calculated from data on two commercial tablets

TABLE IV—Effect of Salt form on the Dissolution and Availability of Tolbutamide⁵

Form of Tolbutamide	In vitro Dissolution rate (hanging pellet) mg/cm²/hr. pH=1	Differences in Blood Sugar (mg/100 ml) in 23 Normal Subjects after two hours—oral dose of 1 g
Free acid	0.21	7.0
Sodium salt	1069	23.7

acids are freely soluble at low pH as they enhance solubility by producing their own local buffer system. Probably on leaving the immediate environment of the solid the dissolved drug is reprecipitated as the acid form, but in the form of very fine particles. These will dissolve more readily owing to their large surface area. The oral hypoglycaemic agent tolbutamide is a good example of a weakly acidic drug administered as the sodium salt, and hypoglycaemic effect and dissolution rate are both greater for this form (Table IV).

CRYSTALLINE FORM (POLYMORPHISM)

Several drugs can exist in more than one crystalline form, each with its own thermodynamic stability; the most unstable polymorph is preferred as this will have the most rapid dissolution rate (Table V). The optimum polymorphic form can often be prepared by

TABLE V—Effect of Crystal Form on Dissolution of Methylprednisolone⁵

Dissolution Test	Dissolution Rate mg/cm²/hr		% Difference in Rates
	polymorph I	polymorph II	
In vitro hanging pellet	0.09	0.14	42
In vivo pellet implant in rats	0.018	0.03	51

judicious use of crystallization conditions, addition of impurities, or melting and cooling cycles. Nevertheless, the formulator must ensure that the unstable form does not revert to the more stable form during storage.

SOLVATION

Drugs may also exist as solvated and non-solvated forms, which will have different solubilities—and hence different dissolution rates. The most common type of solvation is by water—that is, the hydrate. Nevertheless, solvated forms are not necessarily more soluble than non-solvated forms, or vice versa. Thus the anhydrous form of ampicillin has the highest solubility, dissolves more rapidly, and gives the greatest availability (Table VI).

The differences in availability shown in Tables V and VI pose an interesting question. In the past how many active compounds have been classified as inactive simply because they were in the

TABLE VI—Effect of Solvation on Dissolution, Aqueous Solubility, and Availability of Ampicillin⁷

Form of Ampicillin	in vitro		in vivo	
	Dissolution rate-time for 50% to Dissolve (min)	Aqueous Solubility 37°C (mg/ml)	Area Under Serum concentration curve (cm ²)	
			Suspension	Capsules
Anhydrous	7.5	10	144	128
Trihydrate	45	8	120	109

wrong crystalline form, solvated state, or indeed particle size? For example, the crystalline forms of chloramphenicol esters are therapeutically inactive, and only the amorphous form, with small particle size, dissolves rapidly enough in the gastrointestinal tract to be hydrolysed to free absorbable chloramphenicol.⁸

PHARMACEUTICAL MANIPULATION

The availability of a drug at the absorption site can be influenced directly by the physical nature of the dosage form. Orally administered formulations will release the active ingredients in the following sequence.

Coated Tablet
Tablet
Capsule
Powder
Suspension
Solution

increasing rate of release

↓

Thus the drug in solution should give the most rapid release. Nevertheless, when formulating a drug there will be other factors to consider, such as: dose regimen; solubility; stability to hydrolysis, oxidation, etc; nauseous taste; cost. In most cases, except in paediatric and geriatric medicine, the solid dosage forms of capsule and tablet are preferred. The effect of the physical state of the dosage form on availability is shown clearly by the data in Fig. 4, and Tables III and VI.

FIG. 4—Effect of dosage form on availability of salicylamide.

OPTIMUM DOSAGE FORM

It is the task of the formulator to design a delivery system that will give the minimum concentration at the site of action needed to elicit a given pharmacological response. For example, let us consider a drug administered orally in the same quantity but by three different delivery systems each with a different release rate (Fig. 5). Formulation 1 will reach the effective concentration well before formulation 2, but formulation 3 will never reach an effective blood level and thus would be inactive. Formulation 1 has a higher effective blood level concentration than formulation 2, which is maintained for longer. Therefore, this would be the dosage form of choice

FIG. 5—Schematic representation of drug availability. The effect of dosage form on drug blood level (same quantity of drug administered orally by three different formulations).

for rapid delivery, provided that the peak in the blood concentration curve did not bring about undesirable side effects.

Therapeutic Non-equivalence of Drugs

For any given drug there will often be differences in biological availability and presumably in clinical responses. Such "therapeutic non-equivalence" of dosage forms may be caused by:

(1) Different dosage forms given by the same route, such as capsules, tablets, etc.; (2) the same type of dosage form made by two or more manufacturers; (3) batch to batch variation in a dosage form made by one manufacturer.

Normally (2) and (3) will exert a lesser effect on availability than (1) but it is important to realise that one cannot assume that the same dosage forms made by different manufacturers will necessarily give the same therapeutic effect. A much-quoted example of non-equivalence is that by Brice and Hammer,⁹ who compared 16 lots of oxytetracycline capsules from 13 different distributors (Fig. 6). Each of the lots was

FIG. 6.—Therapeutic non-equivalence of oxytetracycline capsules.

certified by the Food and Drugs Administration of the United States (F.D.A.), and testing showed that all but one met the standard regulations. However, *in vivo* studies clearly demonstrated that they were far from equivalent to the branded Pfizer product. After these data were reported the F.D.A. ruled that capsules from all distributors except Pfizer were no longer eligible for continued certification.

TABLE VII—Substances Whose Formulation Affects Biological Availability¹⁰

Acetohexamide	Meprobamate	Reserpine
Aminophylline	Methandrostenolone	Secobarbital sodium
Ampicillin	Methylprednisolone	Sodium
Bishydroxycoumarin	Nitrofurantoin	para-aminosalicylate
Chloramphenicol	Oxytetracycline	Spironolactone
Chlortetracycline	Pentaerythritol	Sulphadiazine
Diethylstilboestrol	tetraniatrate	Sulphamethoxazole
Diphenylhydantoin	Penicillin G potassium	Sulphisoxazole
Erythromycin	Penicillin V potassium	Tetracycline
Ferrous sulphate	Penobarbital sodium	Theophylline, ephedrine,
Griseofulvin	Phenindione	and phenobarbital
Hydrochlorothiazide	Phenylbutazone	tablets
Hydrocortisone	Prednisolone	Thyroid
Indomethacin	Prednisone	Tolbutamide
Isoniazid	Quinidine	Warfarin sodium

The drugs which are proved, or are definitely suspect, of having differing availabilities, depending on their source and formulation, are given in Table VII. This list contains a significant proportion of all currently available official drugs.¹⁰ Many of them have been selected by the F.D.A. for biological equivalency study on a "priority basis". They are generally considered as critical drugs—that is, those required to control a disease or to relieve severe disabling conditions. The active principles are relatively insoluble and the drugs are normally administered as tablets or capsules.

Only in a few cases can we make definite suggestions about the causes of differing availability. Thus particle size is known to affect the action of griseofulvin, phenindione, corticosteroids, spironolactone, and tolbutamide; solvation that of ampicillin; physical state that of chloramphenicol; and additives in formulation (excipients) penicillin G and the tetracyclines. Small formulation changes by a Canadian manufacturer of the anticoagulant bishydroxycoumarin led to unexpected clinical problems and a need to adjust the dosage in individual patients.¹¹

Hence it cannot be assumed that a drug formulation from one source is therapeutically equivalent to one from another source until this has been proved. It is to be hoped that all manufacturers will provide the medical and pharmaceutical professions with full data on safety and efficacy when marketing a new drug or reformulating an existing product. There is little in official publications on the question of availability.

The pharmaceutical profession is well aware of the problem of biological availability and the effects of formulation. The in vitro dissolution data on oxytetracycline tablets B.P. (Fig. 7) were obtained recently at our University Pharmacy Department by pharmacists from hospitals in the Birmingham region.

FIG. 7.—The dissolution of oxytetracycline tablets B.P. (Three different distributors.)

TABLE VIII—Correlation of in vitro Dissolution Rate of Tetracycline Hydrochloride with Serum Concentrations and Urinary Excretion in Man¹²

Tetracycline Capsules from four Different Manufacturers	In vitro Dissolution rate-time for 50% to dissolve at pH 1 (min)	Area Under Serum Curve (μg/ml × hrs)	Urinary Excretion (0-8 hr) (mg)
1	5.1	7.7	54
2	41	5.6	39
3	107	5.2	36
4	244	3.2	22

The distinct differences in in vitro dissolution have yet to be compared with therapeutic response, but probably the in vitro data can be correlated with in vivo blood levels. McDonald *et al.*¹¹ have shown already that in vitro dissolution data for four commercial tetracycline capsules can be correlated with serum concentrations and urinary excretion (Table VIII). Moreover, Brice and Hammer⁸ found that oxytetracycline capsules that gave poor serum levels had a slower rate of dissolution in vitro.

Future studies will show whether the problem of therapeutic non-equivalence of drugs is of importance except in a few special cases, such as with the anticoagulants. The data must be examined critically in the light of other factors such as dose regimen, body weight, dietary differences, physiological factors, and the probability that a high proportion of patients fail to follow the dose regimen.

Drugs in Solution

ABSORPTION AND STABILITY

The rate at which a drug will be absorbed will depend on factors such as the nature of the absorbing tissue, the concentration of the drug, and its ionic character. Most drugs are absorbed by a passive diffusional process that depends on the lipid solubility of the drug (pH-partition hypothesis¹³).

That is, the non-ionised neutral molecule will be preferentially absorbed. The permeability coefficient of a membrane (P) can be expressed as¹²

$$P = K_d D/h$$

where K_d is the oil water partition coefficient of the drug, D is the diffusion coefficient for diffusion of the drug in the membrane and

FIG. 8—Effect of pKa on absorption of weak acids in the stomach.

FIG. 9—Effect of partition coefficient on the absorption of barbiturates.

h is the membrane thickness. In formulation we can take into account such factors as molecular weight, shape, and solvation which will affect diffusion, as well as the dissociation constant of the drug (pKa) (Fig. 8), the pH at the absorption site, and the partition coefficient of the unionized form of the drug (Fig. 9). Acidic drugs will be more lipid-soluble and less water-soluble at low pH, while the reverse will be true at high pH. The converse applies to basic drugs. The environmental pH and drug pKa determine the amount of unionized (absorbable) drug. For an acidic drug (HA)

$$\log \{HA\} = \log \{A^{-}\} + pK_a - pH$$

When $pK_a = pH$, 50% of the drug will be ionized and 50% will be unionized.

Although the diffusional and partition characteristics of a drug may be altered to increase its absorption, we must bear in mind that any structural modifications may adversely affect the pharmacological response.

In formulation the main contribution of the pharmaceutical scientist is to design a delivery system that gives the optimum quantity of drug in solution at the absorption site, at the correct time. Hence he must consider also the stability of the drug in solution and possible degradation by the fluids of the gastrointestinal tract. Drugs are known to be unstable at the low pH of the stomach as well as at the higher pH values of the intestine and the blood. The former problem can be solved by enteric coating and the latter by administration parenterally or by mouth on a full stomach.¹⁴

This article is based on a lecture given in the Birmingham course under the title "The Scientific Basis of Clinical Practice" (see B.M.J., 27 November 1971, p. 510).

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Further Reading

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Any Questions?

We publish below a selection of questions and answers of general interest

Atromid-S and Cholecystitis

Is there any evidence that Atromid-S or any other drug is helpful in the treatment of cholecystitis?

There is no reason to believe that Atromid-S would be helpful in the management of cholecystitis. There is no evidence that serum cholesterol levels are related to bile cholesterol levels or that they are elevated in either cholecystitis or cholelithiasis. Atromid-S does not reduce bile cholesterol levels. Thus cholesterol-lowering agents would not be expected to be of value. There have been many attempts to treat gall stones indirectly, including the administration more recently of cholestyramine,¹ chenodeoxycholic acid,² and lecithin.³ However, there is no firm evidence that any of these are effective and there are theoretical arguments to suggest that in the long term they might cause unwanted side effects.

The usual treatment of acute or chronic cholecystitis is surgical. If it is decided to manage the patient medically an antispasmodic and pethidine for relief of pain is advised. Antibiotics such as tetracycline, ampicillin, or rifamide are generally administered, though their efficacy has been questioned⁴.

Notes and Comments

Holiday First-aid Box.—Dr. R. G. BULLOCK (Plymouth, Devon) writes: The answer given to the question about the contents of a holiday first-aid box ("Any Questions?" 30 October, p. 294) contains advice that antihistamine cream should be included. Most dermatologists seem to frown on these preparations nowadays,¹ as they are potent skin sensitizers. If a specific antihistamine action is needed, as in urticaria, then oral administration is as good. If a simple antipruritic action is wanted then crotamiton (Eurax) ointment or lotion is just as effective (or ineffective).

Dr. J. N. ROSENBERG (New Cross Hospital, London S.E.14) writes: I was surprised to see an antihistamine cream included in the holiday first-aid box. The incidence of skin sensitization following topical antihistamines has been put between 5 and 8-8%.² Other well known hazards are photosensitivity and cross sensitivity reactions which may be produced by promethazine and phenothiazines respectively.³

OUR EXPERT replies: The comments on the antihistamine cream are welcomed. Skin sensitization is certainly a danger with repeated and continuing application but surely the risk would be minimal in the casual first-aid application to insect or jelly fish stings, for which it is very effective.

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