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Review Article

Absorption of Implanted Solid Drug

By BERTON E. BALLARD and EINO NELSON†

DRUG ABSORPTION is a subject which is attracting increasing interest in the areas of pharmacy and pharmacology. The technique of solid drug pellet implantation has particular importance in the livestock and poultry fields, in the area of cancer research where carcinogens or potential ones are studied, in theoretical studies involved with solid drug absorption, in endocrinological work, in studies concerned with metabolism and fate of drugs, and in many more areas where a prolonged "continuous infusion" of drug is required.

Recent reviews have summarized much of what is known concerning processes and factors influencing rate of absorption when drugs are administered by several routes. Thus, with respect to gastrointestinal absorption, Schanker (1) has discussed mainly the influence of a drug's dissociation constant and fat solubility on the process, and Wagner (2) has reviewed the influence of solution kinetics. Cooper and Lazarus (3, 4) and Nelson (5) have considered mainly the properties of sustained-release dosage forms intended for oral administration. Absorption following subcutaneous injection has been exhaustively discussed by Schou (6). The paper of Riegelman and Crowell (7) reviews information available on absorption after administration of drug by the rectal route. Past work on percutaneous absorption has been summarized by Gemmel and Morrison (8) and Barr (9). Work on sublingual absorption has been listed by Katz and Barr (10).

Apparently there has been no general review on absorption after implantation of either pure solid drug or solid drug in mixture with either inert or active materials, although brief reviews on specific topics have appeared. These are listed in an Appendix.[1] This review has been prepared in two parts. In the first part are considered the various physiological and physical factors that have been found to influence absorption rate. The second part of the review is presented in the form of an Appendix and lists and gives references to work in which a variety of drugs have been implanted. For simplicity in organization, each part of the review has its own set of references, numbered consecutively. One reason for the organization adopted is that there is much work reported in the literature which merely describes pharmacological effects elicited from the implanted drugs and bears only indirectly on absorption *per se*. This type of work is listed in the Appendix. Also listed in the Appendix are more complete references to some of the subjects discussed in the main body of the review itself.

In some ways, understanding absorption of implanted solid drug is simplified by the physical nature of materials logically administered by this route. Implantation is nearly synonymous with

Received from the School of Pharmacy, University of California Medical Center, San Francisco 22.

† Present address: School of Pharmacy, University of Buffalo, Buffalo 14, N. Y.

[1] EDITOR'S NOTE: The Appendix which is referred to is not published with this review article in THIS JOURNAL. However, copies of it, in mimeographed form, are available on request from the authors, and interested readers should send their written request direct to the authors.

long duration of action and, as a consequence of this, recent work has shown that understanding the absorption process in many cases is reduced to the problem of understanding solution kinetics *in vivo* (11), because release of drug from pellet implant in the usual case is a much slower process than passage of drug across the membrane at the absorption site. Absorption, then, is solution rate limited.

Solution Kinetics.—A number of factors influence the rate of the solution *in vitro* and *in vivo*. Most of these factors have been discussed in detail in recent reviews (2, 11, 12). One of the most important aspects of absorption from implant is the influence of the implant's geometry and how its weight and surface area change with time.

Influence of the Geometry and/or Surface Area of Implant on Absorption.—Apparently Shelesnyak and Engle (13) were the first to recognize that absorption rate was proportional to the surface area of the implant at a given time. This finding has been confirmed since then, without exception, in many investigations. Surface area will decrease with time, and the function describing the rate of decrease is given by the derivative of the expression describing surface area as a function of time with respect to time.

For regular geometric objects, surface area is usually easy to express as a function of the dimensions of the objects. Thus, the surface area, S, of a sphere is given by

$$S = \pi D^2 \qquad \text{(Eq. 1)}$$

If diameter, D, decreases uniformly with time, *cf.* (14–20), then

$$dD/dt = -k \qquad \text{(Eq. 2)}$$

where k is the rate of decrease of diameter with time. On integrating Eq. 2 and evaluating the constant of integration at zero time, the following equation results

$$D = D^0 - kt \qquad \text{(Eq. 3)}$$

where D^0 is the initial diameter. Substituting Eq. 3 into 1 gives

$$S = \pi (D^0 - kt)^2 \qquad \text{(Eq. 4)}$$

as the relationship between surface area and time. The weight, W, of spheres is given by

$$W = \frac{\pi\rho}{6} D^3 \qquad \text{(Eq. 5)}$$

where ρ is the density of the drug. Decrease of weight with time will be given, using Eq. 3

$$W = \frac{\pi\rho}{6} (D^0 - kt)^3 \qquad \text{(Eq. 6)}$$

or by substituting for D^0 in Eq. 6 by its value from Eq. 5

$$W = \frac{\pi\rho}{6} \left[\left(\frac{6\,W^0}{\pi\rho} \right)^{1/3} - kt \right]^3 \qquad \text{(Eq. 7)}$$

Equation 7 solved for k becomes

$$k = \frac{1}{t} \left[\left(\frac{6\,W^0}{\pi\rho} \right)^{1/3} - \left(\frac{6W}{\pi\rho} \right)^{1/3} \right] \qquad \text{(Eq. 8)}$$

Alternatively, the value of k could be found by dividing the difference between initial and final diameter by the length of time in implant. However, in general, weight is measured more accurately than dimensions because of slight surface irregularities and shape distortions. Once k is determined from experimental measurements, it may be substituted back into Eq. 6 or 7, and weight may then be calculated at any time. Further, when the derivative of Eq. 6 is taken, instantaneous absorption rate, dA/dt, with negative sign is given. Thus

$$\frac{dW}{dt} = -\frac{dA}{dt} = -\frac{k\pi\rho}{2} (D^0 - kt)^2 \qquad \text{(Eq. 9)}$$

Data on the absorption of tolbutamide from implanted spheres of this material, as given by Ballard and Nelson (21), serves as an example to illustrate information that can be obtained from some of the preceding equations. Using their data for sphere B (*loc. cit.*), Eq. 6 becomes

$$W = 606\,(1.048 - 0.00245t)^3 \qquad \text{(Eq. 10)}$$

where W is in mg. and t in hours.

Figure 1 is a plot of Eq. 10 and also of Eq. 9. The latter equation with constants evaluated is

$$dW/dt = -4.45\,(1.048 - 0.00245t)^2 \qquad \text{(Eq. 11)}$$

If the implant were cylindrical, then its weight would be given by

$$W = \rho \frac{\pi D^2 h}{4} \qquad \text{(Eq. 12)}$$

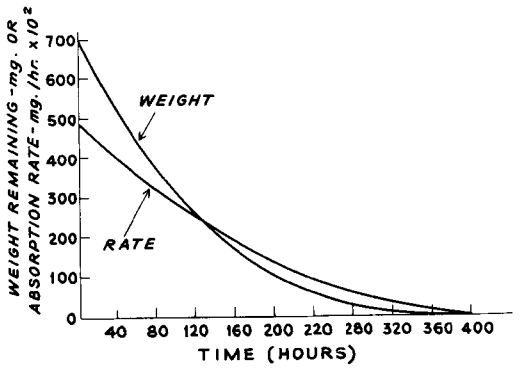

Fig. 1.—Decreases in weight and rate of change of weight as functions of time of an implanted sphere of drug.

where h is its thickness. If the rate of change of thickness and diameter with time were constant then, by same procedure that led to Eq. 3

$$D = D^0 - kt \qquad \text{(Eq. 13)}$$

and

$$h = h^0 - kt \qquad \text{(Eq. 14)}$$

where h^0 is the initial height.

Using Eqs. 13 and 14, Eq. 12 becomes

$$W = \frac{\pi\rho}{4}(D^0 - kt)^2(h^0 - kt) \qquad \text{(Eq. 15)}$$

Determination of the value of k using Eq. 15 is complicated by necessity of obtaining a solution to a cubic equation. However, the solution may be obtained without too much difficulty if a table for the solution of cubic equations, such as that prepared by Salzer, Richards, and Arsham (22), is available.

The rate of change of weight with time is found by taking the derivative of Eq. 15, hence

$$-dW/dt = \rho\frac{\pi k}{4}[(D^0 - kt)^2 + 2(D^0 - kt)(h^0 - kt)] \qquad \text{(Eq. 16)}$$

Equation 15 may be written in terms of the ratio of initial height to initial diameter, *i.e.*, $r = h^0/D^0$, to give

$$W = \frac{\pi\rho}{4}(D^0 - kt)^2(D^0 - kt) \qquad \text{(Eq. 17)}$$

It is of interest to examine the value of Eq. 17 with respect to the value of r. This has been done using data on the absorption of tolbutamide used in the example on absorption from spherical implants. Equation 17 in terms of these data becomes

$$W = 909(D^0 - 0.00245t)^2(D^0 r - 0.00245t) \qquad \text{(Eq. 18)}$$

where W is in mg.

Equation 18 is plotted on Fig. 2 for values of r from 0.1 to 10. This was done by writing Eq. 12 as

$$W^0 = \frac{\rho\pi D^{03} r}{4} \qquad \text{(Eq. 19)}$$

and solving for D^0 at arbitrarily taken values of r. The value of W^0 was that taken from the report previously cited (*loc. cit.*, sphere B). On Fig. 2, all curves shown lie to the left of the curve for a sphere (dotted line) since, for a given material, a sphere has a minimum surface area per unit weight among the various geometric configurations that may be taken. In Fig. 2, the slope of a line at any time is the instantaneous absorption rate. It will be seen in this figure, that for small values of the ratio of thickness to diameter, that absorption rate is nearly constant for most of the time that drug is in implant.

Equations similar to the preceding may be developed easily for other geometric configurations such as oblate and prolate spheroids, etc. Many implants are rod-like with rounded ends, and equations for change in their weight and surface with time would be satisfactorily approximated by the equations for cylinders.

Equation 15 of the preceding has been experimentally verified by Shimkin and co-workers (16) for the case of $h^0 = D^0$. This was done by rearranging this equation to give

$$W^{1/3} = bD^0 - bkt \qquad \text{(Eq. 20)}$$

where $b = (4/\rho\pi)^{1/3}$. Plots of the cube root of weight of implant remaining at various times plotted *vs.* time were linear. They also examined data from work of others wherein $h^0 \neq D^0$ and found that plots of the cube root of weight implant remaining *vs.* time were reasonably linear. Of the various regular geometric objects that would likely be implanted, the implanted cylinder provides the most rigorous test of the assumption made in deriving Eq. 15 and others, *i.e.*, that all dimensions decrease uniformly with time. The work of Shimkin and his co-workers indicates that this assumption is correct (16). The reason that a cylinder provides the most rigorous test is that solution, which is always normal to a surface, is taking place from surfaces normal to each other. The same situation would hold in the case of cubes, for example, but it seems highly unlikely that this object would ever be implanted.

If the intensity of agitation on all faces of a crystalline solid were equal, dimensions would not decrease uniformly if the crystal was anisotropic. This might be a factor to be considered

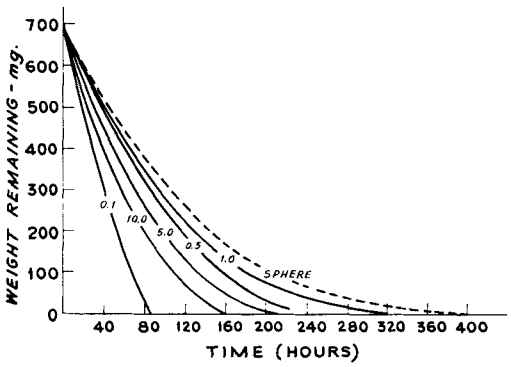

Fig. 2.—Decrease of weight as a function of time for implanted cylinders and a sphere. The numbers by the curves refer to the initial ratio of height to diameter.

with fused implants, but not one with compressed implants. The particles comprising a compressed implant could be expected to be distributed randomly throughout the implant and on its surfaces. The rate of absorption found would be an average representing the arithmetic mean of the rate that would be found for the individual surfaces of the crystal.

It has been reported that absorption of diethylstilbestrol after implantation could be described as a first-order process (23). It seems highly unlikely that this could be the case because absorption of this material is certainly solution rate limited. The result was no doubt an artifact. Many mathematical functions can be roughly fitted to the integrated expression describing a first-order process. For example, if Eq. 15, with constants evaluated for a cylinder with an initial height equal to initial diameter, is used to calculate weight remaining at several times, and values of weight so calculated for the first 100 hours are plotted on semilogarithmic paper as a function of time, the points can be roughly fitted with a straight line. Also, the dimensions given for the apparent first-order rate constant were incorrect.

Body Level of Drug Following Implantation—Mathematical Treatment.—As in the case of any other route of administration, drug absorbed from implant distributes itself in blood and other body fluids and, at the same time, the elimination processes of metabolism and excretion begin. Very little work has been done to express either body level of drug or drug elimination as a function of time in mathematical terms. In many cases, drug elimination may be approximated by considering the process as one whose rate is directly proportional to body level at any time (first order). Assuming this, then the following differential expression should express the rate of change of body level with time when an absorption process is involved

$$\frac{dAb}{dt} = \frac{dA}{dt} - KAb \qquad \text{(Eq. 21)}$$

In Eq. 21, Ab is body level, dA/dt is absorption rate, K is the first-order rate constant for removal of drug from the body, and t is time. If the implant is a sphere, then absorption rate is given by Eq. 9, and if this equation is substituted in Eq. 21, Eq. 22 results

$$\frac{dAb}{dt} = \frac{k\pi\rho}{2}(D^0 - kt)^2 - KAb \qquad \text{(Eq. 22)}$$

Equation 22 may be integrated to give, with constant of integration evaluated at zero time (no drug in the body)

$$Ab = a\left[\frac{(D^0 - kt)^2}{K} + \frac{2k}{K^2}(D^0 - kt) + \frac{2K^2}{K^3} - \left(\frac{D^{0^2}}{K} + \frac{2kD^0}{K^2} + \frac{2k^2}{K^3}\right)\exp\left[-Kt\right]\right] \qquad \text{(Eq. 23)}$$

In Eq. 23 $a = k\pi\rho/2$ and the other terms have been previously defined. The value of the constants in Eq. 23 are all determinable experimentally. Analogous equations based on other implant geometries may also be derived by the procedure shown.

A mathematical treatment similar to the preceding has not been applied to experimentally obtained data. However, drug blood level after implantation of drug has been followed (24–26, 53). In one of these studies (25), pellets of progesterone were implanted both subcutaneously and intrasplenically in mice. Both the free and total progesterone blood levels plateaued after some time following intrasplenic implantation. However, the total progesterone blood level continued to rise after subcutaneous implantation.

In another study, procaine benzylpenicillin tablets were implanted in the vicinity of wounds in human patients undergoing surgery (24). These implantations were either subcutaneous or intramuscular. Penicillin blood level was followed and it was found that, after a few days delay to allow for the attainment of equilibrium, levels fluctuated around a reasonably constant level in a given patient. It was remarked that this method of administering procaine benzylpenicillin was extremely innocuous since no local or general reactions were observed.

In still another study (26), blood level of gold following subcutaneous or intramuscular implantation of pellets of a gold salt in arthritic patients was followed. Measureable quantities of gold were present in blood for many months following implantation.

Absorption and excretion of drug following implantation of spheres has been studied with a different procedure than the one used above to follow absorption (21). It was recognized in this case that absorption from the sphere, which was slow, would eventually become rate limiting in excretion of the drug's metabolite. Thus, for a good part of the time the amount of drug in circulation in the body was small as compared to the amount of drug remaining in solid form in implant and excreted in urine as metabolite. Then the weight of drug in implant at any time should have been given by the Hixon-Crowell cube root law (27) which is

$$W^{0^{1/3}} - W^{1/3} = k't \qquad \text{(Eq. 24)}$$

In Eq. 24, k' was the absorption rate constant whose value depended on solubility of drug at the absorption site, agitation, and other factors. The weight at any time was deducible from the following equation

$$W = W^0 - \frac{Wu}{f} \qquad \text{(Eq. 25)}$$

where Wu was cumulative amount of drug metabolite excreted and f the fraction of a dose of the drug excreted as the metabolite. The quantity Wu was expressible directly in terms of precursor. Substituting Eq. 25 in Eq. 24 gave

$$W^{0^{1/3}} - (W^0 - Wu/f)^{1/3} = k't \qquad \text{(Eq. 26)}$$

When the left hand side of Eq. 26 was plotted as a function of time, a linear relationship was found after a sufficient time had elapsed to allow attainment of equilibrium. The linear relationship indicated the correctness of the assumptions made concerning the absorption, metabolism, and elimination of the drug.

In other work, the kinetics of the excretion of sulfadiazine, following implantation of thin, cylindrical discs of this material in rats, was followed (28). Mean excretion rate over the implantation period was nearly directly proportional to surface area, as estimated by a graphical method (29), at the same time. These results indicated the rate limiting nature of absorption from implants of this drug.

Urinary excretion after implantation of drug has been followed in other work (30). In this instance, 50 mg. of riboflavin with 50 mg. of cholesterol was implanted intramuscularly in two humans. In one patient not deficient in riboflavin, a substantial increase in riboflavin excretion was observed for about 1.5 months. In the other case, the patient was riboflavin deficient and could not be maintained by oral dosage because of severe gastric and intestinal disorders that prevented absorption of this vitamin. The patient could be maintained after parenteral administration of vitamin in solution three times a day, but showed symptoms of deficiency 2 days after cessation of administration. However, after implantation he showed no signs of deficiency for 2 months. Further, his riboflavin excretion was about 10 times greater per day throughout this period than his preimplantation excretion.

Other studies in which drug blood level, excretion of drug or its metabolites, or change in physiological function have been followed after implantation are listed in the Appendix.

Absorption Rate and Surface Area.—It is of interest to consider the relationship between absorption rate and surface area, particularly in regard to the ratio of rate to surface as given in Eq. 27

$$\frac{dA}{dt}\frac{1}{S} = R \qquad \text{(Eq. 27)}$$

In Eq. 27, R is the value of the ratio. For spheres, it is easily shown by Eqs. 4 and 9 that the value of R is given by

$$R = \frac{k\rho}{2} \qquad \text{(Eq. 28)}$$

and R is independent of time.

If the implant is cylindrical in shape, it can be shown by using Eq. 16 and the equation for determining the surface area of this geometric form that the ratio is not a constant, except in one special case, and is, instead, a function of time. This function is given by

$$R' = k\rho\left(\frac{1 + \dfrac{2(h^0 - kt)}{(D^0 - kt)}}{2 + \dfrac{4(h^0 - kt)}{(D^0 - kt)}}\right) \qquad \text{(Eq. 29)}$$

where R' is the function of time. In the special case where initial diameter equals initial height, Eq. 29 reduces to

$$R' = \frac{k\rho}{2} \qquad \text{(Eq. 29a)}$$

and a direct proportionality independent of time exists between absorption rate and surface area of the implant.

A set of widely applied solution rate laws which were written in several forms, depending on initial conditions, are the Hixon-Crowell laws (27). In the several forms of the law, derivations are based on assuming that a direct proportionality exists between surface area and the two-third power of weight of the dissolving substance, which is true among a few common geometric shapes such as spheres, cubes, and cylinders whose initial height equals initial diameter. For the most simple case of dissolution where the object is dissolving in a large enough volume of medium so that the concentration changes may be neglected, the starting equation to derive the law may be written as [a reduced form of the Noyes-Whitney law (31)]

$$dW/dt = -K'S \qquad \text{(Eq. 30)}$$

where K' is constant whose value is a function of several other constants. The physical meanings of these other constants do not bear on the present discussion. When Eq. 30 is rearranged to find the ratio of rate of change of weight (or absorption rate if the process is thought of in terms of rate of change with time of amount of

drug dissolved) to surface area, it will be seen that the resulting equation is of the same form as Eq. 27. If the dissolving solid is a cylinder, then an equation of the same form as Eq. 29 will also express the relationship between rate of weight loss and surface area. Clearly, K' may be a function of time. The Hixon-Crowell laws are in error when any object is considered whose ratio of dimensions change with uniform loss of material from all faces, and this conclusion is explicit from considering Eq. 29.

The reduced form of the Noyes-Whitney law (31) which has been considered in the preceding discussion written for the case of a cylindrical solid undergoing dissolution with uniform loss of all dimensions is, using Eq. 30 and the formula for calculating surface area for a cylinder written in the form that expresses this uniform loss as a function of time

$$-\frac{dW}{dt} = \pi K' \left[\frac{(D^0 - kt)^2}{2} + (D^0 - kt)(h^0 - kt)\right] \quad \text{(Eq. 31)}$$

Equation 31, when integrated, becomes

$$W = \pi K' \left[\frac{(D^0 - kt)^3}{6k} + \frac{(D^0 - kt)(h^0 - kt)^2}{2k} - \frac{(h^0 - kt)^3}{6k}\right] + A \quad \text{(Eq. 32)}$$

where A is the constant of integration. At zero time, $W = W^0$, and when the value of A is evaluated at this time and substituted in Eq. 32 this equation becomes

$$W = W^0 - \pi K' \left[\frac{D^{0^3} - (D^0 - kt)^3}{6k} + \frac{D^0 h^{0^2} - (D^0 - kt)(h^0 - kt)^2}{2k} - \frac{h^{0^3} - (h^0 - kt)^3}{6k}\right] \quad \text{(Eq. 33)}$$

Acidic or Basic Properties and Molecular Weight of the Implanted Drug.—One reason that pellet absorption rate has not been found to correlate well with water solubility, as will be discussed later, is due to the fact the hydrogen ion concentration as well as buffer capacity of the tissue fluids at the site influence the solubility of acidic or basic drugs. These factors have been studied in detail (11).

Absorption rate was assumed to be solution rate limited and expressions derived from Fick's law were obtained to give absorption rate as a function of an acidic or basic drug's dissociation constant, water solubility, and molecular weight. For acidic drugs, experimentally found absorption rates were found to follow, within experimental error, the following equation

$$\frac{dA}{dt} = \frac{cSs}{M^{1/2}}\left(1 + \frac{Ka}{[H^+]_d}\right) \quad \text{(Eq. 34)}$$

In Eq. 34, c is a proportionality constant, M is the molecular weight of a given drug, s is the water solubility of the undissociated acid, Ka the drug's dissociation constant, and $[H^+]_d$ the hydrogen ion concentration of the diffusion layer covering the surface of the implant. This latter quantity was determined by a modification of a method previously used *in vitro* (31). Diffusion layer hydrogen ion concentrations were sometimes substantially different from the hydrogen ion concentrations of the fluids at the implant site, the difference increasing with increasing acidity or basicity of the substances implanted. This is one of the reasons why absorption rate often does not correlate with water solubility.

For basic drugs, the equation appropriate to describe absorption rate was

$$\frac{dA}{dt} = \frac{cSs}{M^{1/2}}\left(1 + \frac{Kb}{[OH^-]_d}\right) \quad \text{(Eq. 35)}$$

In Eq. 35, s is the water solubility of the undissociated base. Equations were also developed for polyfunctional substances (11).

Pellet Density.—Several investigators (14, 32–41) have suggested that pellet density is an important factor influencing absorption rates of implants. It is known that variations in compression pressure used in pellet manufacture affects their densities (or, as some authors put it, their hardness).

Variations in density or compression pressure do affect the weight/area ratio. However, since the absorption rate is directly proportional to the pellet's area exposed to the body fluids at a given time, density alone should not have a direct effect on absorption rate, but only an indirect one in so far as it affects the implant's initial area. In support of this view, Cowie and Folley (17) and Hays, *et al.* (42), have demonstrated *in vivo* that variation of pellet density is a factor of no great importance in implant absorption rate. Parrott, Wurster, and Higuchi (43), correcting for area, have shown *in vitro* that the dissolution rate of spheres was independent of density. They stated that "... although with less dense tablets a greater increment of volume was dissolved per unit time than with the more dense tablets, an equal weight of material was dissolved per unit time from a given surface area for both cases."

In fact, most investigators (17, 44, 45) agree that absorption rates of cast (or fused) and compressed pellets of a given drug are practically the same per unit area. Bishop and Folley (44)

seem to have reversed an earlier claim to the contrary (15).

In more recent work (46) comparing absorption from cast and compressed pellets, it was found that there was no difference when the drug was estradiol. However, compressed desoxycorticosterone acetate pellets were more slowly absorbed than fused pellets. This last result is easily explained if the fusing process produced a more rapidly dissolving polymorphic form of this steroid than the original form that was compressed. Alternatively, the compression process may have produced a more slowly dissolving polymorphic form. Differences in absorption rate between two polymorphic forms of α-methylprednisolone have been observed (11).

In conclusion, the absorption rate and dissolution rate of solid implants are independent of density when corrections are made for area.

Size of Crystals Used in Preparation of Implants.—Soule and Burstein (36) and Greenblatt and Hair (38) asserted that the size of the crystals used in making pellets affects their absorption rate. But Forbes (47) and Hays, *et al.* (42), with experimental evidence, have shown *in vivo* that the size of crystals used in the manufacture of pellets has no effect on absorption rate. The lack of influence of crystal size is most likely due to a factor discussed in a report on some *in vitro* dissolution rate studies (31). Using the equation discussed by Jost (48)

$$Td \cong \sqrt{\eta L/v\rho} \qquad \text{(Eq. 36)}$$

where Td was the thickness of the diffusion layer, η is the viscosity of the medium, L is the linear dimension of surface of solid across which the medium flowed, v was the velocity of flow of the medium as a result of stirring, and ρ was the density of the medium, it was concluded that under the conditions of the experiments, the thickness of the diffusion layer was much greater than the highest point on the pellet's surface (31). Thus, the medium surrounding the pellet was in contact with a diffusion layer of homogeneous composition.

With implanted pellets where the velocity of flow of the medium over the pellet surface is unquestionably much less than the velocity used in the *in vitro* experiments (31), the thickness of the diffusion layer would be large; this can be predicted from Eq. 36. Whether the pellet surface was formed by compression of large or small crystals, or during the fusion process, the diffusion layer is thick enough to mask any of the pellet's minor surface imperfections. Therefore, the absorption rate of compressed pellets should be independent of their method of manufacture, assuming a constant stirring velocity.

Solubility of the Drug.—Deanesly and Parkes (49) were apparently the first to state that the absorption rate of implanted pellets was correlated with the solubility of the substance in body fluids. Others have agreed (32, 33, 50, 51). Biskind, *et al.* (37), stated that the solubility of the compound in various chemical solvents does not influence absorption rate. What they meant by this statement is not clear.

While Lewin and Huidobro (52) could not correlate absorption rate with the water solubility of the drugs they used, they did correlate absorption rate with their experimentally measured serum solubilities.

Influence of Diluents.—It would be expected that the admixture of an inert substance with drug prior to formation of an implant would slow absorption rate of the implant because of the decrease in surface area of drug. On the other hand, it might be expected that, after correction for surface area, diluents could either increase or decrease absorption rate per unit surface area of the implant. If the diluent were a more rapidly dissolving substance than the drug, then drug particles could be expected to be released from the implant with dissolution of the diluent. This process would increase effective surface area of drug. If the drug were a more rapidly dissolving substance than the diluent, then it could be expected that absorption rate per unit area, or even pellet area in some cases, of drug might either remain unchanged or decrease, depending on the relative amounts of drug and diluent. With small amounts of diluent, the diffusion layer would cover the face of the pellet and the absorption site would "see" this area. With large amounts of diluent, as absorption proceeded, drug would have to diffuse to the surface before absorption, and this step could be expected to slow absorption.

The absorption of hexestrol mixed with 25, 49, or 50% lactose has been studied by Cowie and Folley (17). Lactose would be expected to be much faster dissolving than the hexestrol. However, no increase was noted in absorption rate of hexestrol plus lactose as compared to implants of hexestrol alone. With testosterone this was not the case, and the difference in rate became more marked as absorption progressed. This apparent discrepancy can be explained if it is assumed that hexestrol particles were more tightly bound to each other in the implants than were the testosterone particles.

In other work with lactose as a diluent, in amount of 39 to 49%, for hexestrol and diethyl-

stilbestrol, it was stated that absorption was "probably less rapid" with diluent present (54).

Absorption studies of various steroids from implants containing cholesterol have given some unexpected and surprising results. Some of this work has been briefly reviewed by Fuenzalida (55). When a number of steroids were mixed with cholesterol, the absorption of the steroids per unit surface area of drug was very markedly decreased. Further, cholesterol by itself, which is absorbed so slowly that its rate is difficult to measure even in implant studies, was absorbed at measurable rates when a number of steroids were admixed with it. During the course of absorption, the cholesterol-drug ratio did not change (55). These results strongly suggest compound formation between the steroids and cholesterol. It is known that cholesterol forms 1:1 compounds with β-sitosterol, vitamin D_2, and other structurally similar substances, as well as a variety of other substances (56).

Paraffin wax has been used as a diluent to slow absorption of implanted drug (57, 58). Most of the other studies with implants containing inert diluents are listed in the Appendix under cholesterol or the sugars, lactose and glucose. From results obtained in work with implant mixtures, as discussed above and listed in the Appendix, it is rather clear that little quantitative information on the role of the diluent exists.

Phagocytosis.—Forbes (14) and Foss (32) supposed that pellet absorption might be connected with the process of phagocytosis. But after Lewin and Huidobro (52) reviewed the literature on this point, they demonstrated experimentally that implants could be absorbed without the occurrence of phagocytosis. This factor, therefore, does not appear to be important.

Physiological Need of the Animal.—Neither physiological need for the implanted substance nor the animal's sex seems to affect the absorption rates of implants (14, 33, 34, 38, 40, 42, 47, 59–66). These experiments and observations lend support to the view that absorption rate is solution rate limited in the usual case. In the nonsolution rate limited case, absorption rate varies with the difference between the concentration of drug in the implant's diffusion layer and the concentration in the fluids at the membrane in contact with it. The physiological need of an animal might control the concentration of drug in the fluids at the membrane in some cases, but it is explicit in solution rate limited absorption that this concentration is negligible in comparison to the concentration of drug at the pellet's surface. Cholesterol implants serve as a good example of a nonsolution rate limited case of absorption (11).

Site of Implantation and Body Movement.—Statements in the literature regarding absorption rates of implants at various sites in the body are not in agreement. Some authors (14, 36, 38, 50, 51, 54, 67) say that absorption site is important, while others (40, 68, 69) say that absorption rate is essentially independent of the site of implantation. Unfortunately, the statistically significant key experiment which would resolve these opposing views has not been conducted. Reported absorption rates, in the main, are based on results from too few pellets and animals, and the many possible implantation sites have not been systematically studied. It would seem that site of implantation should influence absorption rate because degree of agitation may be different at different sites.

Variations in absorption rate are observed even when a single, carefully defined anatomical region is implanted. Absorption rate varies inversely with the thickness of the diffusion layer surrounding the implant's surface. The thickness of this fluid layer in a particular animal can change with a variation in stirring rate, either due to animal movement or change in flow of interstitial fluid in the region of the pellet.

The clinical variations in absorption rates of desoxycorticosterone acetate pellets observed by McCullagh, *et al.* (70), might well be explained by stirring, and its effect on the thickness of this liquid layer. In this connection, Kearns (71) suggests that the patient massage the area over the implant to increase the rate of absorption.

Encapsulation.—After some drug pellets are implanted for a time, they become surrounded by a fibrous capsule whose morphology and histology have been described (14, 41, 72–75, 84). While many claim that such capsules retard the implant absorption rate (32, 36, 39, 51, 61, 72, 76–83), others think it has no effect (15, 16, 42, 50, 85).

Although no completely convincing experiment has settled this question, the latter view is probably correct because of the solution rate limited nature of absorption from implant. There is evidence (32) that the more rapidly absorbed substances have thicker capsules than the more slowly absorbed ones. Very rapidly absorbed substances do not form capsules, because there is not time enough for the body to form them. The view, which follows, by Shimkin *et al.* (16), seems correct: ". . . it is just as likely that the thickness of the capsule is determined by the slow absorbability of the material rather

than the slowness of absorption being due to the deposition of the surrounding fibrous tissue."

Until more quantitative work is available relating absorption rate of pellets to capsule formation, encapsulation can be disregarded as a factor of major importance.

"Ghost" Formation.—The term "ghost" was coined by Folley (82) who observed that proteinaceous material had infiltrated into the pores of compressed implants. "Ghost" formation was subsequently studied in more detail (15, 17, 42, 45, 52, 54, 65, 83, 86, 87). Some believe that the presence of a "ghost" affects absorption rate (15, 17, 42, 54, 65, 87), while others claim it does not (45, 52). Folley (65), who used hexestrol pellets of differing weights, noted that for small pellets (50 mg.) the correction for the "ghost's" weight made no detectable difference in the absorption rate.

For precise measurements of absorption rate there is no doubt that the weight of the "ghost" should be considered. But whether the "ghost" actually inhibits absorption rate due to plugging of the pellet pores, as some claim, is open to question. On this point two lines of evidence suggest that the "ghost" does not affect absorption rate. (*a*) The absorption rates of cast and of compressed pellets *in vivo* are generally agreed to be the same, as previously discussed, in spite of the fact that the compressed pellet histologically has the more extensive "ghost." (*b*) The *in vitro* studies of Wurster and Seitz (88) have shown that the pores in pellets compressed in air are largely occluded by air and are almost entirely unavailable to the aqueous solvent. One might suppose, then, that the absorption rate of a pellet whose pores are occluded by air or by proteinaceous material would be almost identical.

"Ghost" formation as a factor influencing absorption rate can be considered unimportant. The weight of the "ghost," however, should be accounted for when the weights of pellets are measured after implantation.

Animal's Age.—Forbes (62) observed that the absorption rate of testosterone propionate pellets implanted into young rats decreased during the first 2 months of life. This effect of age on absorption rate may be due in part to the fact that the newborn rat is more responsive to changes in external temperature than older rats (89), and the solubility and rates of diffusion of substances are directly related to temperature. In fact, Deanesly (63) hinted at this when she attributed the different absorption rates of estrone pellets in rats and mice to differences in body temperature or metabolism. Animal physical activity is also a function of the animal's age.

Species Difference.—Very little work has been done to determine species difference in absorption rate. The observation has been made that rats absorb certain drugs after implantation more rapidly than man (46). A comparative study has been done using albino rats, desert rats, and golden hamsters (90). Rate of absorption decreased in the order listed. Species differences are no doubt due to differences in physical activity, body temperature, and composition of the body fluids at the implantation sites.

SUMMARY

Factors that clearly affect absorption rates of implants are their surface area and solubility in body fluids. Factors proposed that do not affect absorption rate greatly (if at all), with the present information, are pellet density (when area corrections are made), crystal size used in implant preparation, phagocytosis, physiological need or sex of the animal, encapsulation, "ghost" formation, and the age of the animal (if it is not young). Factors such as site of implantation and body movement and diluents do have an effect, but little quantitative information is available concerning the magnitude of the effect.

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Research Articles

Study of the Lipid Fraction of Freeze-Dried Dandelion Root

By SALAH ELDIN F. ALI† and EARL P. GUTH

Gas chromatographic studies of the lipid fraction from oven-dried and freeze-dried dandelion root reveal significant difference. Synthesis of fatty acids apparently continues during the oven drying process.

IT IS WELL known that on harvesting an entire plant or removing parts from the plant, many of the vital processes do not stop immediately (1). It is also known that the length of time and the degree of temperature required for drying plant materials affect the rate and intensity of these processes and, consequently, could affect the nature of some constituents normally present. The chemical reactions which occur in plant cells are apparently accelerated by enzymes. Therefore, as long as conditions are favorable to enzymatic action, these reactions will proceed. The rate at which an enzymatic reaction proceeds is influenced not only by the temperature, but also by the length of time that the reaction mixture has been maintained at that temperature. Within limits, an increase in the

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† College of Pharmacy, University of Baghdad, Baghdad, Iraq.