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Historical Perspectives

A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System

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Abstract

Dissolution research started to develop about 100 years ago as a field of physical chemistry and since then important progress has been made. However, explicit interest in drug related dissolution has grown only since the realisation that dissolution is an important factor of drug bioavailability in the 1950s. This review attempts to account the most important developments in the field, from a historical point of view. It is structured in a chronological order, from the theoretical foundations of dissolution, developed in the first half of the 20th century, and the development of a relationship between dissolution and bioavailability in the 1950s, going to the more recent developments in the framework of the Biopharmaceutics Classification System (BCS). Research on relevant fields of pharmaceutical technology, like sustained release formulations, where drug dissolution plays an important role, is reviewed. The review concludes with the modern trends on drug dissolution research and their regulatory implications.

Keywords: Drug dissolution; Bioavailability; Drug release

Contents

1. Introduction

Oral administration of solid formulations has been the major route of drug administration for almost a century. However, it was only 50 or so years ago that scientists realised the importance of dissolution processes in the physiological availability of drugs. In the meanwhile, the study of the dissolution process has been developing since the end of the 19th century by physical chemists. Therefore, most of the fundamental research in the field was not related to drugs at all, and the basic laws for the description of the dissolution process were already available when interest in drug dissolution started to rise.

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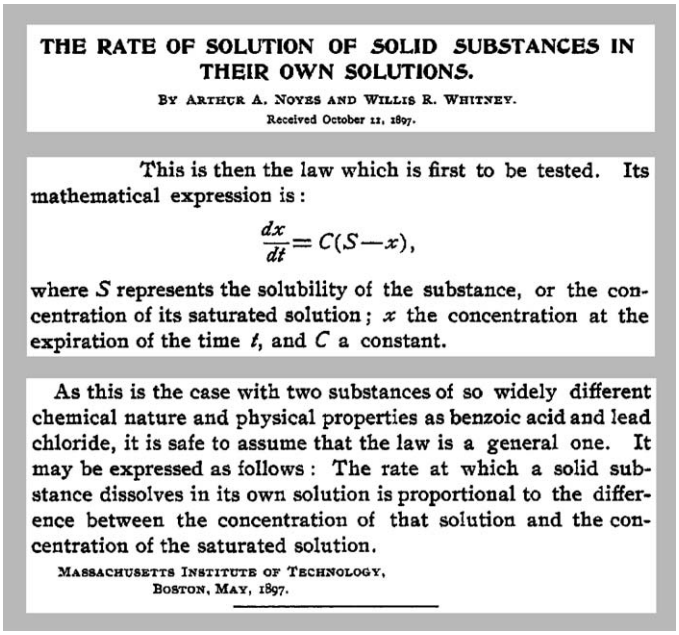
This review attempts to describe the historical evolution of drug dissolution. It places particular emphasis on the fundamental articles in the field, which shaped the major lines of research and regulation policy of the regulatory agencies. Also, parallel research contributions with significant impact on dissolution research are quoted. The present review is structured in chronological order, starting from the first dissolution experiment and the development of the major models for dissolution of solids, moving on to the realization of a relationship between dissolution and bioavailability, which initiated the drug related interest in dissolution, and progressing to the present applications of dissolution studies, with both their scientific and regulatory aspects.

2. 1897–1960: The foundations of dissolution research

In 1897, Noyes and Whitney conducted the first dissolution experiments and published an article entitled "the rate of solution of solid substances in their own solutions" (Noyes and Whitney, 1897). Arthur A. Noyes [1866–1936], was a Professor of Chemistry at MIT and also served as a president of MIT from 1907 to 1909, later moving to Caltech. Together with Willis R. Whitney, they studied the dissolution of two sparingly soluble compounds, benzoic acid and lead chloride. The materials were laid around glass cylinders which were submerged into vessels containing water. The cylinders were rotated at constant speed and under constant temperature. The authors noticed that the rate of dissolution is proportional to the difference between the instantaneous concentration, C at time t, and the saturation solubility, C_S, (Fig. 1). This statement can be formulated mathematically as follows:

$$\frac{dC}{dt} = k(C_S - C) \quad (1)$$



THE RATE OF SOLUTION OF SOLID SUBSTANCES IN THEIR OWN SOLUTIONS.

BY ARTHUR A. NOYES AND WILLIS R. WHITNEY.

Received October 11, 1897.

This is then the law which is first to be tested. Its mathematical expression is:

$$\frac{dx}{dt} = C(S - x),$$

where S represents the solubility of the substance, or the concentration of its saturated solution; x the concentration at the expiration of the time t, and C a constant.

As this is the case with two substances of so widely different chemical nature and physical properties as benzoic acid and lead chloride, it is safe to assume that the law is a general one. It may be expressed as follows: The rate at which a solid substance dissolves in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
BOSTON, MAY, 1897.

Fig. 1. Three extracts from the original article of Noyes and Whitney (1897) showing the title, the main equation and the concluding statement of the article.

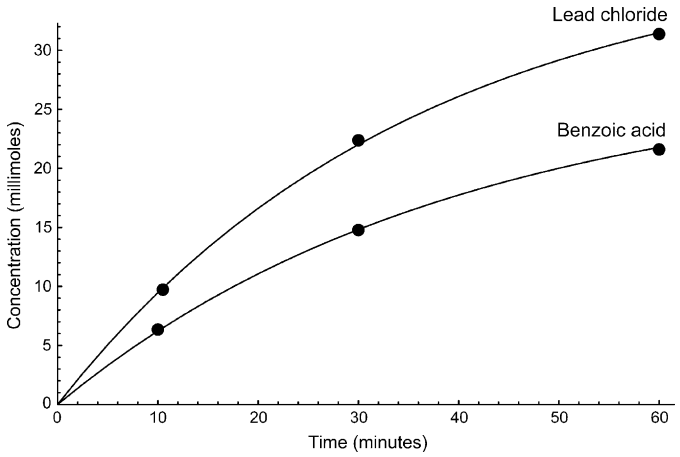


Fig. 2. Concentration–time plots of (Noyes and Whitney, 1897) data together with plots of Eq. (1) using the original estimates for the values of the constants. The data correspond to stick no. 1 for benzoic acid and stick no. 2 for lead chloride.

where k is a constant. The experiment configuration ensured that the surface of the materials was kept constant during dissolution as the materials were in excess of the amount needed to saturate the medium. In Fig. 2 plots of these data together with plots of Eq. (1) using the original estimates for the values of the constants, are shown. The authors attributed the mechanism of dissolution to a thin diffusion layer which is formed around the solid surface and through which the molecules diffuse to the bulk aqueous phase.

The next development came from Erich Brunner, and Stanislaus von Tolloczko at Gottingen, who published an article in 1900 based on a series of experiments that extended the conditions under which Eq. (1) holds and also showed that the rate of dissolution depends on the exposed surface, the rate of stirring, temperature, structure of the surface and the arrangement of the apparatus (Bruner and Tolloczko, 1900). The proposed model was derived from Eq. (1) by letting $k = k_1 S$:

$$\frac{dC}{dt} = k_1 S(C_S - C) \quad (2)$$

where S is the surface area. Also, Brunner in 1904 published a paper based on the work done in his Ph.D. that studied the problem further, trying to find specific relations between the constants involved (Brunner, 1904). This work was published together with the theoretical work of Walther Nernst [1864–1941], who was Professor of Physical Chemistry and the founder and director of the Institute for Physical Chemistry and Electrochemistry at Gottingen where Brunner was working (Nernst, 1904). Walther Nernst was one of the major contributors in the field of physical chemistry, and received a Nobel Prize in 1920 "in recognition of his work in thermochemistry". The main result of this two-part publication of Nernst and Brunner in 1904, which was based on the diffusion layer concept and Fick's second law was what is known as the Nernst–Brunner equation, which was derived from Eq. (2) by letting $k_1 = D/(Vh)$:

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_S - C) \quad (3)$$

where D is the diffusion coefficient, h the thickness of the diffusion layer and V is the volume of the dissolution medium.

In 1931 Hixson and Crowell expressed the surface, S of Eq. (2) in respect to the weight, w, by letting S to be proportional to $w^{2/3}$, which makes the Eq. (2) applicable to dissolving compact objects (Hixson and Crowell, 1931). By this consideration, Eq. (2), when integrated yields an equation which relates time to the cubic-root of weight and in the special case of sink conditions, where small concentrations are considered and the difference $(C_s - C)$ can be considered as constant, the cubic-root law takes a simple form:

$$w_0^{1/3} - w^{1/3} = k_2 t \quad (4)$$

where w_0 is the initial weight and k_2 a constant. In their paper Hixson and Crowell reported that the Noyes–Whitney equation in its original form and without any details about the mechanism of the process had been sufficiently validated with a wide range of experiments, as opposed to the various mechanistic explanations that had appeared, none of which was entirely satisfactory.

The above approaches can be categorized as various expressions of the diffusion layer model as a physical explanation for dissolution process, where the limiting step has been considered to be the diffusion of molecules through a stagnant film of liquid around the solid surface. By the 1950s two more alternative explanations were available as reviewed by Higuchi (1961). The interfacial barrier model, considered that interfacial transport, rather than diffusion through the film, is the limiting step due to a high activation energy level for the former. This model was first proposed by Wilderman (1909) and was also considered by Zdanovskii (1946), but has not been studied in detail and an explicit mathematical description for the dissolution kinetics is not available, while variations have also appeared (Miyamoto, 1933). The third model for dissolution is Danckwerts' model, which appeared in 1951 (Danckwerts, 1951). According to this, constantly renewed macroscopic packets of solvent reach the solid surface and absorb molecules of solute, delivering them to the solution. Combinations of these models were also considered. The work of Levich improved the theoretical model of the dissolution experiment using rotating disks, taking into account the centrifugal force on diffusion (Levich, 1962).

Despite the advances in in vitro dissolution in chemical engineering sciences, in the pharmaceutical sciences the concept was not used extensively until the early 1950s. Until then the in vivo availability of the drug was thought to be determined solely by the disintegration of the tablet, ignoring the dissolution process. Many in vitro procedures to determine the disintegration time of tablets were suggested, at the time, and some of them were reviewed by Morrison and Campbell (1965). The first official disintegration test for tablets was published in the Pharmacopeia Helvetica in 1934, which used water at 37 °C as the medium and periodical shaking, while in the United States Pharmacopeia the disintegration test was introduced in the 14th edition in 1950. Other methods, developed later, tried to introduce more realistic conditions, using, for example, simulated gastric fluids as media for the disintegration experiments. One of the most sophisticated introduced an artificial stomach with simulated in vivo conditions, including pH level, peristalsis and the presence of food (Filleborn, 1948). In the early 1950s it became clear that disintegration alone could not account for the physiological availability of drugs and in many cases the dissolution rate was, instead, the limiting step.

3. 1950–1980: The development of a relationship between dissolution and bioavailability

To the best of authors' knowledge, Edwards in 1951 was the first to appreciate that following the oral administration of solid dosage forms, if the absorption process of drug from the gastrointestinal tract is rapid, then the rate of dissolution of that drug can be the step which controls its appearance in the body. In fact, he postulated that the dissolution of an aspirin tablet in the stomach and intestine would be the rate process controlling the absorption of aspirin into the blood stream (Edwards, 1951). However, Nelson in 1957 was the first to explicitly relate the blood levels of orally administered theophylline salts to their in vitro dissolution rates (Nelson, 1957). He used a non-disintegrating drug pellet, (mounted on a glass side so that only the upper face was exposed), placed at the bottom of a 600 mL beaker in such a manner that it could not rotate when the dissolution medium was stirred at 500 rpm.

In mid 1960s to early 1970s a number of studies demonstrating the effect of dissolution on the bioavailability of a variety of drugs were reported in the literature. Two reports were published in 1963 and 1964 drawing attention to the lack of full clinical effect for two brands of tolbutamide marketed in Canada (Campagna et al., 1963; Levy et al., 1964). These tablets were shown to have long disintegration times as well as slow dissolution characteristics (Levy, 1964). Besides, a slight change in formulation of an experimental tolbutamide preparation was shown to produce significantly lower blood levels and hypoglycemic effect (Varley, 1968). In 1968, Martin et al. (1968) reported significant differences in the bioavailability between different brands of sodium diphenylhydantoin, chloramphenicol and sulfisoxazole. MacLeod et al. (1972) reported greater than 20% difference in peak concentration and area under the serum concentration–time curve for three ampicillin products.

In late sixties it was realized that differences in product formulation could lead to large differences in speed of onset, intensity and duration of drug response. At that time the term "bioavailability" was coined to describe either the extent to which a particular drug is utilized pharmacologically or, more strictly, the fraction of dose reaching the general circulation. The most dramatic bioavailability examples have been with digoxin in the U.K. and the USA in 1971 and phenytoin in Australia and New Zealand in 1968.

In the former case, different formulations of digoxin yielded up to sevenfold differences in serum digoxin levels (Lindenbaum et al., 1971). These observations prompted the FDA in collaboration with the late John Wagner to carry detailed dissolution studies on 44 lots from 32 manufacturers of 0.25 mg digoxin tablets available in the 1972 North American market-place (Skelly,

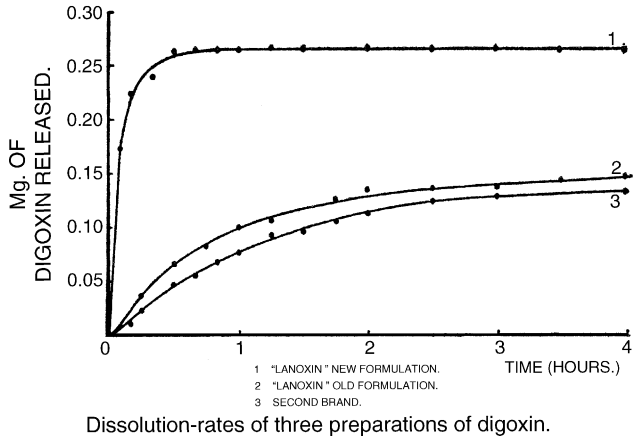


Fig. 3. Dissolution profiles of three different formulations of digoxin, exhibiting large differences, reprinted from (Fraser et al., 1972) with permission.

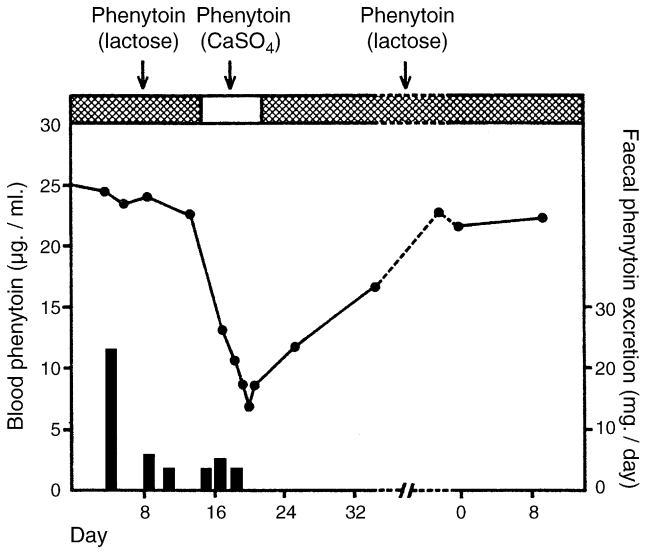


Fig. 4. Plot of blood phenytoin concentrations, reprinted with permission from (Tyrer et al., 1970), including the original legend.

solution profiles of the digoxin products and substantiated the view that either lot-to-lot or amongst brands bioinequivalence originates from differences in dissolution rates. Additional dissolution studies conducted in other laboratories confirmed these findings (Fraser et al., 1972). In Fig. 3 dissolution profiles of different formulations of digoxin are shown from (Fraser et al., 1972) exhibiting large differences.

Phenytoin toxicity occurred in a large number of patients when the manufacturer replaced the excipient calcium sulfate with lactose in immediate release phenytoin tablets (Tyrer et al., 1970). Initially, the lower extent of absorption of phenytoin in the presence of calcium sulfate was ascribed to the formation of an insoluble calcium-phenytoin salt, Bochner et al. (1972). However, Chapron et al. (1979) found no effect when they studied the influence of calcium on bioavailability of phenytoin administering calcium gluconate before, with and after a single dose of 300 mg of phenytoin. These results indicated that the higher hydrophilicity of lactose compared to calcium sulfate, promoted the dissolution rate of phenytoin resulting in higher bioavailability and consequently higher concentrations of phenytoin in plasma, exceeding its narrow therapeutic range of 10–20 μg/mL. The results of this study are shown in Fig. 4. A decade later, loss of seizure control occurred in a patient on phenytoin was related to altered dissolution characteristics caused by the physical changes of phenytoin capsules (Cloyd et al., 1980).

3.1. 1970: Initiation of the official dissolution tests

All of the above bioavailability concerns prompted the introduction of dissolution requirements in tablet and capsule monographs in pharmacopeias. Of equal significance was the recognition of the immense value of dissolution testing as a tool for quality control. Thus, equivalence in dissolution behaviour was sought in light of both the bioavailability and quality control considerations throughout the last 35 years.

As mentioned above a number of studies mainly in the USA during the 20-year period 1950–1970 shed light on the importance of pharmaceutical ingredients and processes in regard to the dissolution–bioavailability relationship. As a result of these

was adopted as an official dissolution test in 6 monographs of the *United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*) in 1970. Due to the continuous intense interest in the subjects of dissolution and gastrointestinal absorption, an explosion in the number of monographs of the dissolution requirements in subsequent USP/NF editions was noted (Table 1). Remarkable events during this evolution are the adoption of the paddle method (USP apparatus 2) in 1978, the publication of a general chapter on *Drug Release* in USP 21 (1985), the presence of 23 monographs for modified-release dosage forms in USP 22-NF 18 (1990), the adoption of the reciprocating cylinder (USP apparatus 3) for extended-release products in 1991 and the adoption of the flow-through cell in (USP apparatus 4) for extended-release products in 1995.

It should also be noted that the first guidelines for dissolution testing of solid dosage forms were published in 1981 as a joint report of the Section for Official Laboratories and Medicines

Table 1
Number of monographs in the US Pharmacopeia and the National Formulary which require dissolution or release tests

Edition/year	Monographs for immediate-release dosage forms	Monographs for modified-release dosage forms	
		Extended	Delayed
USP 18-NF 13/1970	6	–	–
USP 19-NF 14/1975	12	–	–
USP 20-NF 15/1980	60	–	–
USP 21-NF 16/1985	400	1	–
USP 22-NF17/1990	462	18	5
USP 23-NF18/1995	501	6	25
USP 24-NF19/2000	552	26	14
USP 29-NF24/2006	619	38	14

Control Services and the Section of Industrial Pharmacists of the FIP (FIP, 1981).

3.2. Research on factors affecting the rate of drug dissolution

During the early stages of drug dissolution research (1950–1960) and in particular after dissolution was established to be an important factor in the bioavailability of certain drugs, the detailed study of factors affecting the dissolution rate were studied extensively.

The degree of agitation is one of the important factors determining dissolution. Generally, higher stirring rates result in higher dissolution rates. This was studied quantitatively as well and several publications appeared, that gave experimental evidence of a power law relationship between dissolution rate and stirring rate (Wurster and Taylor, 1965). Under certain conditions this power-law collapsed to an almost linear relationship.

Dissolution rate depends also directly on solubility, as the Noyes–Whitney equation (Eq. (1)) suggests. This became of particular importance as the influence of solubility on bioavailability was considered to come primarily from its influence on dissolution rather than saturation of GI fluids. This is so, because sink conditions were considered to prevail inside the intestines, at least for highly permeable drugs (Wurster and Polli, 1961; Gibaldi and Feldman, 1967). It was also realized that solubility can be affected by the presence of solubilizing agents in the dissolution medium either by partitioning of the drug into the micelles of a surfactant or complexation of the drug with one or more substances. The seminal articles of Bates et al. (1966) on griseofulvin dissolution and Tao et al. (1974) on cholesterol dissolution in bile salt solutions can be considered as the initiatory studies on drug dissolution in micellar solutions. Also, in 1968 the publication of the book "solubilization by surface-active agents and its applications in chemistry and the biological sciences" marked the new very rapidly growing field (Elworthy et al., 1968). A method called "solid dispersion formulation" was also developed in order to enhance the dissolution rate of sparingly soluble compounds. The drug is dispersed in an inert hydrophilic carrier, which promotes the dissolution of drug through its high wettability. Dispersion of chloramphenicol in urea is one of the first classic examples (Chiou, 1971).

Another factor that influences the dissolution rate is the surface exposed in the solvent. This is primarily affected by the particle size, meaning the smaller the particles, and therefore in greater number, the higher their total exposed surface compared to larger but fewer particles of the same total mass. The effect is especially dramatic with poorly soluble compounds as, for example, digoxin which showed 100% increase in bioavailability when its particle size was reduced from 100 μm to approximately 10 μm (Jounela et al., 1975). Studies on the effect of particle size were reviewed by Levy (1963). However, the relationship of particle size–surface area–dissolution rate is not always straightforward. Finholt (1974) clearly demonstrated that if the drug is hydrophobic and the dissolution medium has poor wetting properties, reduction of particle size may lead to a smaller (1974) reported that when granules containing phenacetin in different particle sizes were prepared using gelatine as a hydrophilic diluent their dissolution rate was found to increase as the particle size was progressively decreased. On the contrary, when simple phenacetin particles were tested for their dissolution in 0.1N HCl, the dissolution rate increased as the particle size increased. The situation was altered returning to normality, when a surface active agent Tween 80 was added to the dissolution medium. The anomalous behaviour was attributed to the better wetting of larger particles in comparison to the smaller particles, which floating on the medium exposed a smaller surface area to the medium. The addition of surface active agent restored the normal situation by improving the wetting of particles. Similar results were obtained with phenobarbital and aspirin (Finholt, 1974).

During this period an important contribution to the mathematical modelling of dissolution curves was published by Langenbucher (1972). He observed that if one plots the quantity $-\ln(1-m)$ versus time on a log–log plot, where m is the accumulated fraction of dissolved material, the curve looks linear, and one can then perform linear regression. This is equivalent to fitting a Weibull equation to the dissolution data:

$$m = 1 - \exp\left[\frac{-(t-T)^b}{a}\right] \tag{5}$$

where t is time, T a lag time, a a scale constant and b is a shape constant.

4. 1980s: Dissolution becomes an essential tool for the development and evaluation of sustained release formulations

The first mention of a constant release oral medication is quoted in a British patent almost 70 years ago (Lipowski, 1934). In 1952, Smith Kline and French introduced the first time-released medicine, Dexedrine (dextroamphetamine sulfate). It was marketed and used in a Spansule—a novel form of drug delivery (Blythe et al., 1959). Since then the term sustained release is in common usage to describe orally administered products that modulate the time course of drug concentration in the body by releasing the drug over extended time periods. The selection of a drug candidate for the design of a sustained release system depends on various criteria such as short biological half-life ($t_{1/2}$), narrow therapeutic index, efficient GI absorption, small daily dose and marketing benefits. Theeuwes and Bayne were the first to derive in 1977 a relationship between $t_{1/2}$, the optimum therapeutic range blood level, $C_{max} - C_{min}$, and the dosing interval, T, assuming a one-compartment model with repetitive intravenous injections at pseudo-steady state (Theeuwes and Bayne, 1977):

$$T \leq 1.44 \cdot t_{1/2} \ln \frac{C_{max}}{C_{min}} \tag{6}$$

4.1. Kinetics of drug release

Since late 1970s the development of sustained release deliv-

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