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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

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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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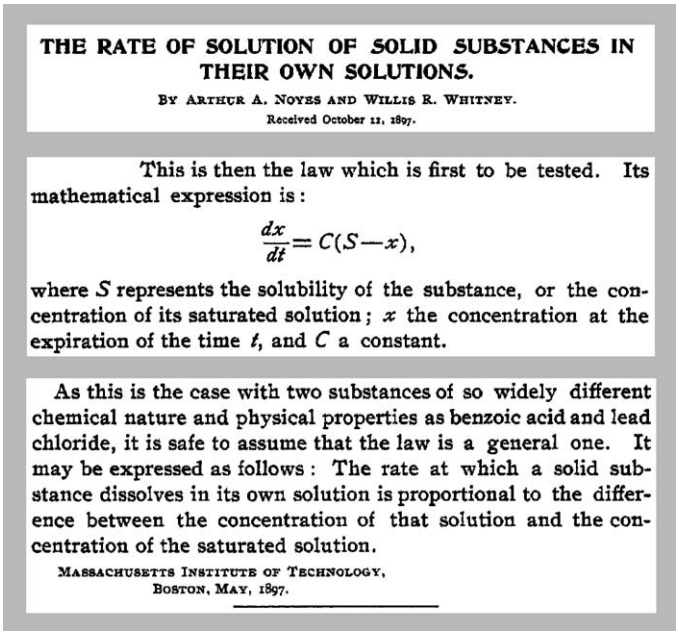
This review attempts to describe the historical evolution of drug dissolution. It places particular emphasis on the fundamental articles in the field, which shaped the major lines of research and regulation policy of the regulatory agencies. Also, parallel research contributions with significant impact 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. Reprinted with permission.

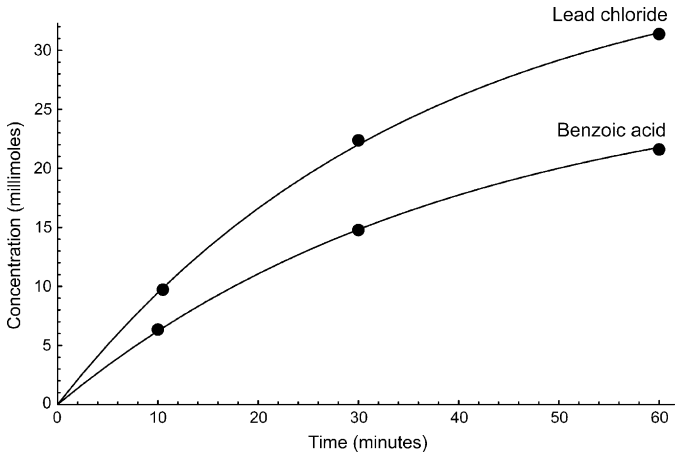


Fig. 2. Concentration–time plots of (Noyes and Whitney, 1897) data together with plots of Eq. (1) using the original estimates for the values of the constants. The data correspond to stick no. 1 for benzoic acid and stick no. 2 for lead chloride.

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:

$$w_0^{1/3} - w^{1/3} = k_2 t \tag{4}$$

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 was Filleborn's method which was published in 1948 and 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, 1988). The studies revealed tremendous differences in the dis-

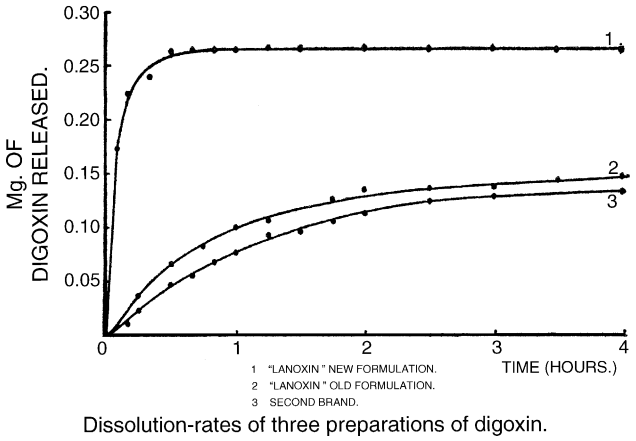


Fig. 3. Dissolution profiles of three different formulations of digoxin, exhibiting large differences, reprinted from (Fraser et al., 1972) with permission.

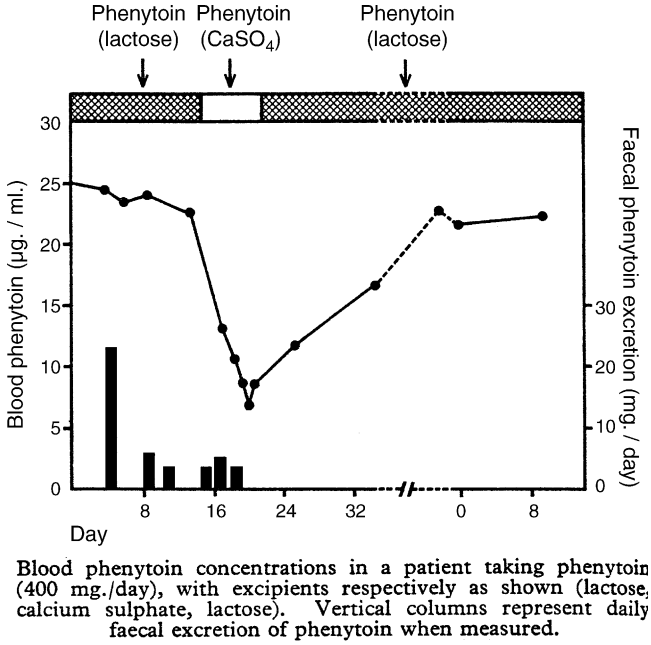


Fig. 4. Plot of blood phenytoin concentrations, reprinted with permission from (Tyrer et al., 1970), including the original legend.

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 developments, the basket-stirred-flask test (USP apparatus 1) 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 effective surface area and a slower dissolution rate. Finholt (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 delivery systems evolved rapidly. The basic performance requirement

of these systems is that they release drug in vivo according to a predictable rate. The kinetics of drug release follows the operative release mechanism of the system, e.g., diffusion through inert matrix, diffusion across membrane or hydrophilic gel, osmosis, ion-exchange, etc. By far, diffusion is the principal release mechanism, since apart from the diffusion-controlled systems, diffusion takes place at varying degrees in both chemically and swelling-controlled systems.

Solute release models preceded the development of drug delivery systems by many years. In fact, the mathematical modelling of drug release from diffusion-controlled systems relies on the Higuchi model published in 1961 (Higuchi, 1961). He analyzed the kinetics of release from an ointment assuming that the drug is homogeneously dispersed in the planar matrix and the medium into which it is released acts as a perfect sink under pseudo steady-state conditions. Higuchi derived Eq. (7) for the cumulative amount $q(t)$ of drug released at time t:

$$\frac{q(t)}{q_\infty} = K\sqrt{t} \tag{7}$$

where q_∞ is the cumulative amount of drug released at infinite time and K is a composite constant with dimension time$^{-1/2}$ related to drug diffusional matrix as well as the design characteristics of the system. Due to the approximate nature of Eq. (7), its use for the analysis of release data is recommended only for the first 60% of the release curve ($(q(t)/q_\infty) \leq 0.60$).

In late 1960s, Wang et al. published an article which can be considered as the initiator of the realization that two apparently independent mechanisms of transport, a Fickian diffusion and a case II transport, contribute in most cases to the overall drug release (Wang et al., 1969). The former mechanism is governed by Fick's law, while the latter reflects the influence of polymer relaxation on the molecules' movement in the matrix (Enscore et al., 1977). Some years later, Fu et al. (1976) used a mechanistic model to study the release of a drug homogeneously distributed in a cylinder. In reality, Fu et al. solved Fick's second law equation assuming constant cylindrical geometry and no interaction between drug molecules.

In 1985, a date which marks the initial rapid phase of growth of delivery systems, Peppas (1985) introduced a semi-empirical equation (the so-called power law) to describe drug release from polymeric devices in a generalized way:

$$\frac{q(t)}{q_\infty} = K_1 t^n \tag{8}$$

where K_1 is a constant reflecting the structural and geometric characteristics of the delivery system expressed in time^{-n} units and n is a release exponent the value of which is related to the underlying mechanism(s) of drug release (Ritger and Peppas, 1987). Again, valid estimates for K_1 and n can be derived from the fitting of Eq. (8) to the first 60% of the experimental release data. Detailed discussions of the assumptions of the derivations of Eqs. (7) and (8) in relation to their valid applications to real data can be found in literature (Siepmann and Peppas, 2001; Macheras and Iliadis, 2006). Since Eqs. (7) and (8) enjoy a wide applicability in the analysis of drug release studies, caution should be exercised for their proper use in relation to the elucidation of the release mechanisms (Rinaki et al., 2003b).

Through the years a plethora of mechanistic release models have been published in literature (Siepmann and Peppas, 2001; Macheras and Iliadis, 2006). Although the mechanistic models are more physically realistic, their mathematical complexity is their main disadvantage for wide use. In recent years, Monte Carlo simulations following the pioneering work of Bunde et al. (1985) were used to study drug release from Euclidean (Siepmann et al., 2002, 2004; Kosmidis et al., 2003b) or fractal spaces (Kosmidis et al., 2003a). The work of (Kosmidis et al., 2003a,b) demonstrated that the Weibull function (Eq. (5)), is the most powerful tool for the description of release kinetics in either Euclidean or fractal spaces. Based on these findings, a methodology was developed (Papadopoulou et al., 2006) for the elucidation of release mechanisms using the entire set of data and the estimate for the exponent b of time.

4.2. In vitro in vivo considerations

The major objective in the design of an oral controlled release formulation is to achieve little or no effect of the GI environment upon the rate of drug release. This is a rather difficult goal since the formulation traverses a varying milieu: from a pH close to 1 in the fasted stomach through the duodenum (pHs 4–5) and a gradually increasing intestinal pH reaching the alkaline region in the distal section of the intestinal tract. In parallel, these formulations can be dosed either in presence or absence of food and the dramatic physiological changes, e.g., pH, bile and pancreatic secretions can influence the rate of drug release. Overall, this complex-heterogeneous GI environment has a greater impact on drug dissolution for controlled release formulations than that observed with conventional preparations. Based on this realization a separate general chapter, *Drug Release* ⟨724⟩ was adopted in the USP 21-NF 16 as early as 1985 providing methodology and acceptance criteria for extended-release and delayed-release products (see Table 1).

Dilantin®, an extended-release product of Parke Davis was the first to have an approved dissolution specification attached to it as a condition of lot-to-lot approval by the FDA. Shah et al. (1983) proposed a dissolution window over time to distinguish the two types of Dlantin® formulations (100 and 300 mg) and ensure lot-to-lot bioequivalence. During the same time, two quinidine gluconate formulations, Quinaglute Duratabs® (Innovator brand, Berlex) and an unapproved and marketed product were found to have quite similar dissolution characteristics despite of the fact that they were bio-inequivalent (Prasad et al., 1982). The similarity of dissolution profiles was justified in 0.1N HCl as well as in 0.1N HCl for the first hour and then in pH 7.4 for seven additional hours. Further dissolution studies (Skelly et al., 1986) in a wide range of pH values (1.0–7.4) revealed significant differences in the dissolution profiles at the intermediate pH values (2.6–5.8) when the percent (dissolved) was plotted as a function of pH and time in a 3D plot (topographical dissolution characterization).

During the early days of 1980s, several reports in literature (Pedersen, 1981; Lagas and Jonkman, 1983; Pedersen and

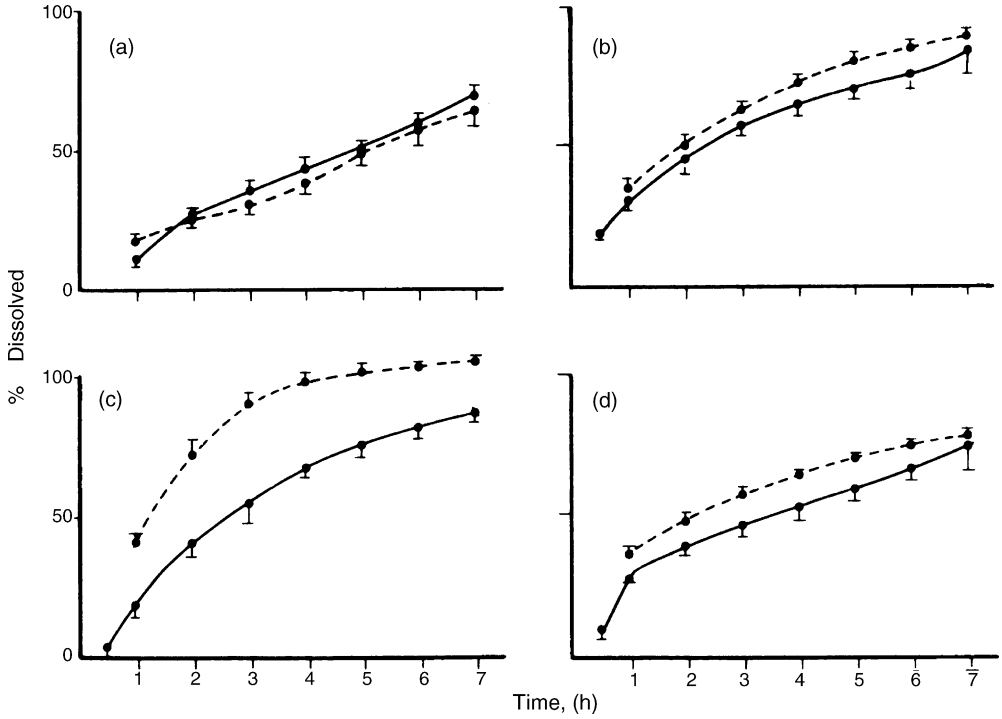


Fig. 5. Theophylline dissolution curves from one of the first studies of drug dissolution in food mimicking media. (a) Theo-dur (theophylline), (b) Phyllotemp (aminophylline), (c) Xantair (choline theophyllinate) and (d) Choledyl (choline theophyllinate) tablets, in milk (solid) and phosphate buffer, pH 6.5 (dashed), at 37 °C. Reprinted from (Macheras et al., 1987) with permission.

Moller-Petersen, 1984; Hendeles et al., 1985) indicated that food induced changes in theophylline absorption from a number of marketed controlled release formulations. These absorption changes were associated with formulations exhibiting either pH-dependent or pH-independent dissolution characteristics while the fat content of the meal was considered as the major determinant of the so-called "dose dumping". Since then the term "food effect" was coined and its importance is reflected in the specific requirement for its assessment in the evaluation of bioequivalence of controlled release formulations (FDA, 2002). At that time, a variety of in vitro methodologies based on dissolution tests using media such as oleic acid, sodium deoxycholate and milk were developed for predicting "food effect" under in vitro conditions (Wearley et al., 1985; Maturu et al., 1986; Macheras et al., 1987, 1989). In Fig. 5, theophylline dissolution curves from one of the first studies of drug dissolution in food mimicking media (Macheras et al., 1987), are shown. These articles can be considered as the progenitors of most subsequent work on bio-relevant dissolution media published a decade later.

5. 1980–2000: Emphasis on dissolution as a prognostic tool of oral drug absorption

Drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors and physiological variables including regional permeability differences, pH, luminal and mucosal enzymes, and intestinal motility among others. Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption (Macheras and Iliadis, 2006).

In 1985, Amidon and co-workers, using a pseudoequilibrium model, made a major step in the theoretical analysis of oral drug absorption when solubility and dose were taken into account for the estimation of the absorption potential (AP) of a drug, apart from the pH-partition hypothesis parameters (lipophilicity, and degree of ionization) (Dressman et al., 1985). Four years later a quantitative version of the absorption potential concept was published (Macheras and Symillides, 1989) which enabled the estimation of the fraction of dose absorbed as a function of AP. However, the microscopic model based on mass balance considerations and published in 1993 can be considered as a landmark in the history of oral drug absorption since it revealed the three fundamental parameters, namely, dissolution, absorption and dose numbers, which control the extent of oral drug absorption (Oh et al., 1993). As a matter of fact, two differential equations, expressed in dimensionless variables, were used to describe the dissolution of drug particles and the uptake of the dissolved drug. This work enabled Amidon et al. (1995) to develop in their seminal paper published in 1995 a Biopharmaceutics Classification System (BCS). According to BCS a substance is classified on the basis of its aqueous solubility and intestinal permeability, and four drug classes were defined i.e., high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III), low solubility/low permeability (Class IV). The properties of drug substance were combined with the dissolution characteristics of the drug product, and predictions with regard to the in vitro–in vivo correlations for each of the drug classes were pointed out.

These advances attracted the obvious interest of scientists in the importance of dissolution tests as predictors of oral absorp-

tion for Class II drugs. In an attempt to establish correlations between the results of the dissolution tests and the in vivo absorption data, artificial fluids, simulating gastric and small intestinal conditions in the fasted state, were developed (Dressman et al., 1998). Also, media mimicking the fed state conditions in the human intestinal fluid were proposed (Dressman et al., 1998; Galia et al., 1998; Kostewicz et al., 2002; Persson et al., 2005). In some cases (Pedersen et al., 2000; Kostewicz et al., 2002; Persson et al., 2005) the in vitro dissolution rate of poorly soluble drugs in simulated media in the fasted state do not always correlate with the dissolution rate in aspirated intestinal fluids.

Although all these studies contribute to the proper selection of representative media mimicking gastric and small intestinal conditions, the simulation of the in vivo hydrodynamic conditions remains an insuperable obstacle. This is particularly so since recent studies based on computational fluid dynamics (McCarthy et al., 2003, 2004; D'Arcy et al., 2005) revealed not only the complexity of the fluid flow in the everyday use of basket and paddle methods of dissolution, but also the chaotic aspects of hydrodynamics (D'Arcy et al., 2006). These results in conjunction with the complexity of (i) gastrointestinal drug absorption phenomena (Macheras and Argyrakis, 1997) and (ii) the heterogeneous in vivo conditions (Weitschies et al., 2005) indicate that we are far away from the simulation of the in vivo hydrodynamics and the proper design of a really prognostic dissolution test.

6. 2000–present: Dissolution in the framework of BCS

The FDA guidance (FDA, 2000) on BCS issued in 2000 provides regulatory benefit for highly permeable drugs that are formulated in rapidly dissolving solid immediate release formulations. The guidance classifies a substance to be highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1–7.5, while a drug product is defined as rapidly dissolving when no less than 85% of the dose dissolves in 30 min using USP Apparatus I at 100 rpm in a volume of 900 mL in 0.1N HCl, as well as in pH 4.5 and 6.8 buffers. Thus, petitioners may request biowaivers for high solubility-high permeability substances (Class I) formulated in immediate release dosage forms that exhibit rapid in vitro dissolution as specified above.

The reference of the FDA guidance exclusively to "the highest dose strength" for the definition of highly soluble drugs implies that a drug is always classified in only one class regardless the possible different performance in respect to solubility of smaller doses used in actual practice. However, this is not in accord with the dose dependency (non-Michaelian type) of oral drug absorption, which consistently has been demonstrated in the early (Dressman et al., 1985; Macheras and Symillides, 1989) and recent studies (Boxenbaum, 1999; Sanghvi et al., 2001; Willmann et al., 2003, 2004; Faassen and Vromans, 2004; Rinaki et al., 2004). Moreover, the dissolution criteria of the FDA guidance have been characterized as conservative (Kaus et al., 1999; Yu et al., 2002) and suggestions for broadening them have been pointed out (Polli et al., 2004). In a similar vein, the high solubility definition of the FDA guidance on BCS has been criticized by Yazdanian et al. (2004) as too strict for acidic drugs and they also quote "an inherent limitation of the solubility classification is that it relies on equilibrium solubility determination, which is static and does not take into account the dynamic nature of absorption". Their remarks were based on the fact that several non-steroidal anti-inflammatory drugs exhibit extensive absorption despite their classification in Class II of the BCS. These experimental observations were explained by Rinaki et al. (2004) utilizing simulations for the in vivo drug dissolution and wall permeation. However, two recent studies (Kasim et al., 2004; Lindenberg et al., 2004) provide results of provisional classification of the drugs contained on the WHO Essential Drugs List and the top 200 drugs lists from the US, GB, ES, JP and suggest that for more than 60% of oral immediate release drug products on the market today, bioequivalence may be regulated based on dissolution testing.

It should be noted that dissolution specifications of the FDA guidance are not correlated with the drug's solubility/dose ratio, which has been shown to control the rate of drug dissolution (Rinaki et al., 2003a). It was Lansky and Weiss (1999) who raised a question on this issue for the first time in 1999, and soon after dose was incorporated explicitly into the fundamental relationships used routinely in dissolution (Rinaki et al., 2003a; Dokoumetzidis et al., 2006). These advances are important for the quantitative aspects of biopharmaceutics drug classification (Rinaki et al., 2003c) as well as the in vivo dissolution modeling approaches used to interpret the extensive absorption of Class II drugs (Rinaki et al., 2004). In addition, the extent of drug dissolution is either directly or indirectly associated to the solubility/dose ratio assuming the diffusion layer model (Dokoumetzidis et al., 2006). These findings have both theoretical and practical interest since they indicate that dissolution data contain explicit information regarding the solubility of drug and therefore can be in principle used as sole indicators for biopharmaeutic drug classification.

7. Conclusion

Dissolution research started to develop in 1897 when Noyes and Whitney derived their equation in the course of their dissolution studies on benzoic acid and lead chloride. Thus, dissolution started as a topic in physical chemistry, and is still an important subject of research in various sections of physical sciences (Avnir, 1989). The history of the study of dissolution, outlined here, makes it clear that the quantitative aspects of the subject have been dependent on input from the physical scientists Noyes and Whitney, Hixson and Crowell and Levich. Also, the work of Weibull in statistics had a remarkable impact on the quantitative analysis of dissolution data.

Alongside that, during the past 35 years, dissolution studies have become an essential part of drug applications to regulatory bodies worldwide. In this regard, dissolution tests are used in the pharmaceutical industry for quality control and to assist with the determination of bioequivalence. Besides, the dissolution tests provide useful information at several stages of drug development. Although scientists wish to establish in vitro–in vivo correlations between release of drug from the formulation and

drug absorption, the limited knowledge of the complex composition and hydrodynamics of the gastrointestinal fluids remains a real hurdle. The experience gained so far indicates that the design of a unique dissolution test to be used reliably as a prognostic tool of oral drug absorption will not appear in the near future.

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