Doi: 10.1111/j.1742-7843.2009.00506.x
Journal compilation © 2009 Nordic Pharmacological Society. *Basic & Clinical Pharmacology & Toxicology*, **106**, 168–172

MiniReview

Biopharmaceutical Classification Based on Solubility and Dissolution: A Reappraisal of Criteria for Hypothesis Models in the Light of the Experimental Observations

Georgia Charkoftaki, Aristides Dokoumetzidis, Georgia Valsami and Panos Macheras

Laboratory of Biopharmaceutics-Pharmacokinetics, Faculty of Pharmacy, University of Athens, Athens, Greece

(Received 1 September 2009; Accepted 17 September 2009)

Abstract: The diffusion layer model of drug dissolution is used for the simulation of oral drug absorption as well as for the analysis of experimental data. The governing role of saturation solubility in the rate of dissolution makes this parameter predominant for biopharmaceutical classification purposes. The hypothesis models and criteria associated with the use of solubility and dissolution for the biopharmaceutical classification of compounds and marketed drugs are reviewed in this article. The complex hydrodynamics in the *in vitro* dissolution apparatuses as well as the motility in the gastrointestinal tract do not allow the application of the diffusion layer model in these systems, as this has been built and verified in the rotating disk device. The solubilizing capacity of gastrointestinal fluids media is higher than the aqueous saturation solubility usually reported and used for biopharmaceutical purposes. Emphasis is given on the reaction-limited model of dissolution which provides a useful alternative not based on diffusion principles. Model independent dissolution parameters are more useful for regulators as our knowledge for the dissolution mechanism(s) under *in vivo* conditions is limited.

Scientific research is based on data interpretation. This task is usually accomplished with the classical hypothesis-model-fitting exercise; the results of the model fitting to the data lead to either the verification or the rejection of the hypothesis associated with the model employed (fig. 1). This type of studies has been extensively applied in biopharmaceuticals with a special emphasis on the gastrointestinal absorption of drugs [1–5]. These studies have demonstrated that the solubility and dissolution rate, together with the intestinal absorptive potential of a drug (permeability) are of major importance for the bioavailability of a drug. In this context, the tube model [3] which considers constant permeability along the intestines, a plug flow fluid with the suspended drug particles moving with the fluid, and dissolution in the small particle limit has been used for the development of the biopharmaceutical classification system [6]. According to the biopharmaceutical classification system as well as the relevant FDA guidance [7] on biowaiver of *in vivo* bioavailability and bioequivalence, a substance is classified in one of four drug classes on the basis of its aqueous solubility and intestinal permeability.

However, several concerns have been raised for the permeability classification of drugs, and a biopharmaceutical drug disposition classification system based on the extent of drug metabolism has been proposed [8,9]. Similarly, several reports in the literature indicate either the conservatism of solubility-dissolution criteria [10–12] or suggest other approaches for solubility-dissolution classification [13–16].

In this work, we re-assess the fundamental assumptions used for solubility and dissolution in respect of the biopharmaceutical classification of drugs taking into account the relevant experimental *in vitro* and *in vivo* observations.

The Basic Hypothesis: Drug Dissolution Follows the Diffusion Layer Model

Background.
Dissolution research began more than a century ago [17]. The dissolution process of a solid drug is mainly described by eq. (1), the so-called Noyes-Whitney equation [18] and its modified form of Nernst and Brünner [19,20]:

$$\frac{dC}{dt} = k(C_s - C) \tag{1}$$

where k is the dissolution rate constant, C_s is the saturation solubility of drug and C is the concentration of the bulk fluid at time t. Eq. (1) relies on the diffusion layer model which assumes that a thin diffusion layer is formed around the solid surface and through which the dissolved drug molecules diffuse to the bulk aqueous medium. In reality, dissolution is a heterogeneous process which takes place in two steps: (i) a reaction at the solid-liquid interface (interfacial transport) and (ii) transfer of the dissolved species through

Author for correspondence: Panos Macheras, Faculty of Pharmacy, University of Athens, Panepistimiopolis 157 71, Athens, Greece (fax +30 210 7274027, e-mail macheras@pharm.uoa.gr).

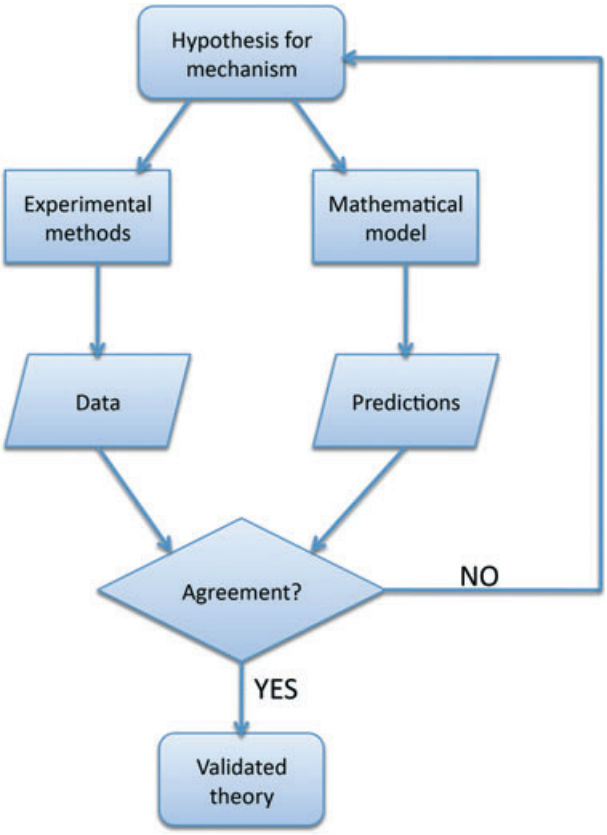

Fig. 1. Development of new scientific theory is based on hypothesis testing and validation through experiments. Mathematical modelling based hypothesis testing fits very well within this context and helps to validate, refine or even reject altogether the hypothesis. In situations of a well founded verification of the hypothesis, the model can be used as a basis for the construction of a scientifically based guideline in the relevant field.

the diffusion layer to the bulk aqueous phase. Thus, eq. (1) is used to describe drug dissolution when the rate of diffusion of the species is much slower than the reaction at the solid-liquid interface. The extensive use of eq. (1) in biopharmaceutics is associated with its mathematical simplicity and the governing role of saturation solubility in the rate of drug dissolution. However, recent articles [21,22] provide a detailed description of the conditions and assumptions associated with the use of eq. (1).

Hydrodynamic conditions.
According to Levich [23], eq. (1) represents a theoretically sound expression only for diffusional flow in a static medium and not in a medium in motion. For this reason, Levich [23] developed the theory of convective diffusion of solute in liquids and derived relationships for the thickness of the diffusion layer and the agitation rate of the rotating disk apparatus [24]. In parallel, a series of fluid dynamic models [21] rely on diffusion principles and the assumption of the unstirred fluid layer, too.

Most of the studies dealing with the diffusion layer model are performed in the rotating disk device where the surface area and the hydrodynamic conditions are perfectly controlled. The results of these studies clearly demonstrate the predominant role and effect of agitation conditions on the rate of drug dissolution. However, these results cannot be extrapolated to the official dissolution tests as recent studies based on computational fluid dynamics revealed the complexity of the fluid flow in these systems [25–27]. Needless to say that dissolution results in various official dissolution tests differ because of the differences in agitation rate. Moreover, the variable and heterogeneous conditions and volume content of the gastrointestinal fluids [28,29] are extremely dissimilar if compared with the flow of liquid in the rotating disk device.

Saturation solubility – supersaturated dissolution data.
According to eq. (1), the saturation solubility is the driving force of the dissolution rate. A variant of eq. (1) has also been used in the seminal biopharmaceutical classification system work [6] and therefore it is not surprising that the biopharmaceutical classification system adopts the aqueous solubility for classification purposes. This development induced a plethora of solubility and dissolution studies for Class II drugs which exhibit dissolution-limited absorption using media most akin to the *in vivo* conditions. One of the avenues followed in this field of research is the study of the solubility and dissolution properties of poorly soluble drugs in either food-mimicking media, for example milk [30,31] or biorelevant media [31–33]. Alternatively, human aspirates were used to study drug solubility and dissolution in the gastrointestinal tract [34–37]. Although most of the lipophilic drugs were found to be more soluble in milk than in aqueous media [30,31], the solubility of danazol and felodipine in HCl under- or over-estimates their intragastric solubilities, respectively [34,35]. Overall, the solubility data in human gastric aspirates have high intra- and inter-subject variability [34] while the solubilizing capacity of human intestinal fluids in the fed state is strongly time-dependent [37]. This type of variability is inherently associated with the dynamics of the processes in the gastrointestinal tract, which cannot be mimicked under *in vitro* conditions, and is one of the reasons for the failure of IVIVC [38].

Eq. (1) and its variants are also unsatisfactorily applied when supersaturated dissolution data are encountered. These dissolution curves exhibit an initial rapid increase to a concentration maximum followed by a progressive diminution towards a steady-state value, usually corresponding to the saturation solubility of the drug in the dissolution medium used [39,40]. This type of dissolution curves are observed when solid dispersion formulations and co-precipitates of drugs with polymers are used. Also, non-monotonic dissolution curves are observed when the drug exhibits polymorphism. In this case, only one of its forms is the most thermodynamically favourable at a given temperature, the one having the lowest Gibbs energy. During the dissolution process, there is a concentration increase to a maximum value, then a solution-mediated transformation takes place (i.e. from anhydrous to hydrate form) and finally the solution

is stabilized to a steady-state value, where the form with the lowest Gibbs energy dominates [41]. However, several reports in the literature provide conclusive evidence of supersaturated dissolution profiles for compounds which do not exhibit polymorphism, such as amorphous itraconazole particles [42]. Supersaturated dissolution behaviour for inorganic compounds for example metal oxides with no polymorphism or phase transitions has been reported, too [43].

Recent studies dealing with kinetic solubility and supersaturated phenomena [44,45] place particular emphasis on the relevance of supersaturated solubility with the biopharmaceutic classification of drugs. Moreover, supersaturated solubilities are frequently found in studies measuring drug concentrations in human aspirates while the subsequent precipitation of drug has been the subject of several studies [46,47]. Again, the analysis of supersaturated-precipitation dissolution data using the Nernst-Brünner modified form of eq. (1) failed unavoidably [47].

Overall, the dynamics of the *in vivo* supersaturated phenomena as well as the *in vivo* hydrodynamics are insuperable obstacles for mimicking drug solubility-dissolution under *in vitro* conditions. These observations indicate 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.

Reaction-Limited Model of Dissolution: An Overlooked Alternative

Recently, the long history of the 'interfacial barrier model' or 'reaction-limited model' in dissolution was reviewed [22]. Its limited use in drug dissolution is due to the prevalence of the rotating disk apparatus in the mechanistically driven dissolution studies. The mild and fully controlled agitation conditions of the rotating disk experiments favour the predominance of the slower step, namely, the diffusion of dissolved drug molecules over the interfacial transport. Even the reactive terms in diffusion-convective equations used in rotating disk experiments are considered instantaneous and ignored. However, as it was mentioned above, the hydrodynamics and by logical extension the drug's dissolution mechanism(s) in the rotating disk device are different from the various official dissolution apparatuses as well as the gastrointestinal lumen.

Although Miyamoto [48] explained the classical Noyes-Whitney relationship using Boltzman's thermodynamic principles as early as in 1933; a well founded mathematical model for reaction-limited dissolution has not been proposed until recently. During the last 10 years or so, three reaction-limited approaches which do not rely on premises of diffusion principles were reported [22,49,50]. The most recent of these approaches [22] is based on the bidirectional chemical reaction of the undissolved drug species with the free solvent molecules yielding the dissolved of drug complex with solvent. The rate of dissolution is driven by the concentration of undissolved species and the saturation solubility corresponds to the concentration when the reaction equilibrium is reached. In that work [22], the model equation developed was applied successfully to dissolution data sets measured in official apparatuses. Also, the governing role of the saturation solubility in the dissolution process associated with the diffusion layer model was not verified [22]. This observation underlines the importance and the potential of application of reaction-limited approaches in the simulation of oral drug absorption where classical diffusion principles are not applicable due to the heterogeneous composition and structure-function of the gastrointestinal tract [28,29].

Biopharmaceutical Classification of Drugs Based on Solubility and/or Dissolution

Since the mid 1980s, there has been emphasis on the approaches correlating the drug's biopharmaceutical properties with the fraction of dose absorbed. The first approach for a biopharmaceutical drug classification was published in 1989; the estimate of the drug's 'absorption potential' was used for the classification of drugs in three categories [1]. Later on, Oh and coworkers [3] using the tube model revealed that three fundamental parameters, namely dissolution, absorption and dose numbers, control the extent of oral drug absorption. The latter approach has been the basis for the formulation of Biopharmaceutics Classification System [6]. Each substance is classified on the basis of its aqueous solubility and intestinal permeability and four drug classes were defined: high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability drugs (Class IV). According to the FDA relevant guidance [7], a substance is classified as highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH 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 0.1 N HCl, as well as in pH 4.5 and 6.8 buffers.

As the dissolution process in the biopharmaceutical classification system article has been modelled with a modified form of the Noyes-Whitney equation [18–20], the dominant role of the aqueous solubility has been mirrored in the classification and the biopharmaceutical classification system guideline [7]. However, our knowledge of the exact dissolution mechanisms under *in vivo* conditions is limited; thus, dissolution-based instead of solubility-based classifications have been proposed for new molecular entities [15,16] and marketed drugs [15]. In this vein, model-independent dissolution criteria such as mean dissolution time [15] and intrinsic dissolution rate [16] have been proposed for dissolution classification. Moreover, the dissolution criteria of the FDA guideline [7] have been found extremely conservative [15]. As the present criteria [7] for solubility and dissolution refer to 250 and 900 ml, respectively, the harmonization of the volumes into a single volume of 500 ml has been proposed [15].

Overall, the use of the aqueous solubility for biopharmaceutical classification is questionable if one takes into

account the plethora as well as the time dependence of supersaturated *in vivo* data published in the literature in conjunction with our uncertainty of the dissolution mechanism(s) operating under *in vivo* conditions. As a dissolution experiment provides information about the solubility of a drug as well, dissolution-based classification should be favoured in the future. Also, model independent criteria should be preferred, for example percentage of dose dissolved at a given time point or the mean dissolution time provided that the constraints of the physiological system are taken into account, for example mean intestinal transit time. What is implicit from all above is that we are far away from a well founded interpretation based on *in vitro* and *in vivo* data of gastrointestinal absorption using the classical hypothesis-model loop of fig. 1. More research is required to advance our knowledge in this field of research in order to achieve a valid interpretation of data and build more meaningful criteria in scientifically based guidelines. However, the current strict solubility and dissolution criteria of the guideline [7] simply ensure that the regulation policy remains on the safe side.

References

1 Macheras PE, Symillides MY. Toward a quantitative approach for the prediction of the fraction of dose absorbed using the absorption potential concept. Biopharm Drug Dispos 1989;**10**:43–53.

2 Sinko PJ, Leesman GD, Amidon GL. Predicting fraction dose absorbed in humans using a macroscopic mass balance approach. Pharm Res 1991;**8**:979–88.

3 Oh D-M, Curl RL, Amidon GL. Estimating the fraction absorbed from suspensions of poorly soluble compounds in humans: a mathematical model. Pharm Res 1993;**10**:264–70.

4 Kalampokis A, Argyrakis P, Macheras P. Heterogeneous tube model for the study of small intestinal transit flow. Pharm Res 1999;**16**:87–91.

5 Kalampokis A, Argyrakis P, Macheras P. A heterogeneous tube model of intestinal drug absorption based on probabilistic concepts. Pharm Res 1999;**16**:1764–9.

6 Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995;**12**:413–20.

7 FDA/CDER. Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Washington, DC, August 2000.

8 Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 2005;**22**:11–23.

9 Benet L, Amidon G, Barends D, Lennernas H, Polli J, Shah V *et al.* The use of BDDCS in classifying the permeability of marketed drugs. Pharm Res 2008;**25**:483–8.

10 Yazdanian M, Briggs K, Jankovsky C, Hawi A. The "high solubility" definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs. Pharm Res 2004;**21**:293–9.

11 Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP *et al.* Biopharmaceutics classification system: the scientific basis for biowaiver extensions. Pharm Res 2002;**19**:921–5.

12 Rinaki E, Dokoumetzidis A, Valsami G, Macheras P. Identification of biowaivers among class II drugs: theoretical justification and practical examples. Pharm Res 2004;**21**:1567–72.

13 Rinaki E, Valsami G, Macheras P. Quantitative biopharmaceutics classification system: the central role of dose/solubility ratio. Pharm Res 2003;**20**:1917–25.

14 Fagerholm U. Evaluation and suggested improvements of the biopharmaceutics classification system (BCS). J Pharm Pharmacol 2007;**59**:751–7.

15 Papadopoulou V, Valsami G, Dokoumetzidis A, Macheras P. Biopharmaceutics classification systems for new molecular entities (BCS-NMEs) and marketed drugs (BCS-MD): theoretical basis and practical examples. Int J Pharm 2008;**361**:70–7.

16 Zakeri-Milani P, Barzegar-Jalali M, Azimi M, Valizadeh H. Biopharmaceutical classification of drugs using intrinsic dissolution rate (IDR) and rat intestinal permeability. Eur J Pharm Biopharm 2009;**73**:102–6.

17 Dokoumetzidis A, Macheras P. A century of dissolution research: from Noyes and Whitney to the Biopharmaceutics Classification System. Int J Pharm 2006;**321**:1–11.

18 Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc 1897;**19**:930–4.

19 Nernst W. Theorie der reaktionsgeschwindigkeit in heterogenen systemen. Z Phys Chem 1904;**47**:52–5.

20 Brünner E. Reaktionsgeschwindigkeit in heterogenen systemen. Z Phys Chem 1904;**47**:56–102.

21 Sugano K. Theoretical comparison of hydrodynamic diffusion layer models used for dissolution simulation in drug discovery and development. Int J Pharm 2008;**363**:73–7.

22 Dokoumetzidis A, Papadopoulou V, Valsami G, Macheras P. Development of a reaction-limited model of dissolution: application to official dissolution tests experiments. Int J Pharm 2008;**355**:114–25.

23 Levich V. Physicochemical Hydrodynamics. Prentice Hall, Englewood Cliffs, NJ, 1962.

24 Wood JH, Syarto JE, Letterman H. Improved holder for disk intrinsic dissolution rate studies. J Pharm Sci 1965;**54**:1068.

25 D'Arcy DM, Corrigan OI, Healy AM. Evaluation of hydrodynamics in the basket dissolution apparatus using computational fluid dynamics-dissolution rate implications. Eur J Pharm Sci 2006;**27**:259–67.

26 D'Arcy DM, Healy AM, Corrigan OI. Towards determining appropriate hydrodynamic conditions for in vitro in vivo correlations using computational fluid dynamics. Eur J Pharm Sci 2009;**37**:291–9.

27 Kakhi M. Mathematical modeling of the fluid dynamics in the flow-through cell. Int J Pharm 2009;**376**:22–40.

28 Macheras P, Argyrakis P. Gastrointestinal drug absorption: is it time to consider heterogeneity as well as homogeneity? Pharm Res 1997;**14**:842–7.

29 Weitschies W, Wedemeyer RS, Kosch O, Fach K, Nagel S, Söderlind E *et al.* Impact of the intragastric location of extended release tablets on food interactions. J Control Release 2005;**108**:375–85.

30 Macheras PE, Koupparis MA, Antimisiaris SG. Drug binding and solubility in milk. Pharm Res 1990;**7**:537–41.

31 Galia E, Nicolaides E, Hörter D, Löbenberg R, Reppas C, Dressman JB. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res 1998;**15**: 698–705.

32 Kostewicz ES, Brauns U, Becker R, Dressman JB. Forecasting the oral absorption behavior of poorly soluble weak bases using solubility and dissolution studies in biorelevant media. Pharm Res 2002;**19**:345–9.

33 Ghazal HS, Dyas AM, Ford JL, Hutcheon GA. In vitro evaluation of the dissolution behaviour of itraconazole in bio-relevant media. Int J Pharm 2009;**366**:117–23.

34 Vertzoni M, Pastelli E, Psachoulias D, Kalantzi L, Reppas C. Estimation of intragastric solubility of drugs: in what medium? Pharm Res 2007;**24**:909–17.
35 Pedersen BL, Müllertz A, Brøndsted H, Kristensen HG. A comparison of the solubility of danazol in human and simulated gastrointestinal fluids. Pharm Res 2000;**17**:891–4.
36 Dressman JB, Vertzoni M, Goumas K, Reppas C. Estimating drug solubility in the gastrointestinal tract. Adv Drug Deliv Rev 2007;**59**:591–602.
37 Clarysse S, Psachoulias D, Brouwers J, Tack J, Annaert P, Duchateau G *et al.* Postprandial changes in solubilizing capacity of human intestinal fluids for BCS class II drugs. Pharm Res 2009;**26**:1456–66.
38 Dokoumetzidis A, Macheras P. IVIVC of controlled release formulations: physiological-dynamical reasons for their failure. J Control Release 2008;**129**:76–8.
39 Bani-Jaber A, Hamdan I, Al-Khalidi B. Sodium mefenamate as a solution for the formulation and dissolution problems of mefenamic acid. Chem Pharm Bull 2007;**55**:1136–40.
40 Matteucci ME, Paguio JC, Miller MA, Williams 3rd RO, Johnston KP. Highly supersaturated solutions from dissolution of amorphous itraconazole microparticles at pH 6.8. Mol Pharm 2009;**6**:375–85.
41 Florence AJ. The solid state. In: Florence TA, Siepman J (eds). Modern Pharmaceutics, Vol. 1. Basic Principles and Systems. Informa Healthcare, New York, 2009;253–310.
42 Matteucci ME, Paguio JC, Miller MA, Williams Iii RO, Johnston KP. Flocculated amorphous nanoparticles for highly supersaturated solutions. Pharm Res 2008;**25**:2477–87.
43 Schmidt J, Vogelsberger W. Dissolution kinetics of titanium dioxide nanoparticles: the observation of an unusual kinetic size effect. J Phys Chem B 2006;**110**:3955–63.
44 Box KJ, Völgyi G, Baka E, Stuart M, Takács-Novák K *et al.* Equilibrium versus kinetic measurements of aqueous solubility, and the ability of compounds to supersaturate in solution-A validation study. J Pharm Sci 2006;**95**:1298–306.
45 Box KJ, Comer JE. Using measured pKa, logP and solubility to investigate supersaturation and predict BCS class. Curr Drug Metab 2008;**9**:869–78.
46 Kostewicz ES, Wunderlich M, Brauns U, Becker R, Bock T, Dressman JB. Predicting the precipitation of poorly soluble weak bases upon entry in the small intestine. J Pharm Pharmacol 2004;**56**:43–51.
47 Sugano K. A simulation of oral absorption using classical nucleation theory. Int J Pharm 2009;**378**:142–5.
48 Miyamoto S. A theory of the rate of solution of solid into liquid. Trans Faraday Soc 1933;**29**:789–94.
49 Dokoumetzidis A, Macheras P. A population growth model of dissolution. Pharm Res 1997;**14**:1122–6.
50 Lánský P, Weiss M. Does the dose-solubility ratio affect the mean dissolution time of drugs? Pharm Res 1999;**16**:1470–6.

