

The Solubility Did Not Move at All, and the Dissolution Became a Thousand Times Faster

— the same substance, the same **100** mg: going from **1** mm to **1** μm takes the surface area from **5.0×10^{-4}** to **5.0×10^{-1}** m^2 — and the time to **90** per cent from **49.34** hours to **2.96** minutes — “poorly soluble” names two different quantities — [Paper 386]

Yuuki YAMAGISHI (山岸 勇輝)
Yamagishi Complexity Torus Lab, Japan
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— *From thinking to syncing.* —

Abstract

When a drug is called “poorly soluble”, two different quantities are being called by one name. This paper shows that one of them can be moved by a factor of a thousand while the other does not move at all—milling does not change the solubility. No new theorem or law is claimed. First, at fixed mass the surface area is $A = 6m/(\rho d)$, inversely proportional to particle size (Section 2). Second, taking 100 mg from 1 mm to 1 μm raises the area from 5.0×10^{-4} to 5.0×10^{-1} m^2 , exactly **1000** times (Section 2). Third, and this is the core of the paper. The time to 90 per cent falls from **49.34** hours to **2.96** minutes, and the solubility does not move at all (Section 3). Fourth, the number of particles goes from **159** to **1.591549×10^{11}** , exactly **1000** times per decade of size (Section 2). Fifth, the speed is set by geometry and the solubility by thermodynamics; a mill touches only the former (Section 4). Sixth, the separator is “how much dissolves at equilibrium” versus “how long it takes to get there” (Section 5).

Scope of this paper (scope note): No new theorem or law is claimed—the Noyes–Whitney equation, the relation between specific area and particle size, and the improvement of dissolution by milling are all known in pharmaceuticals. No drug is designed—no formulation or dose is given. Only the independence of two quantities is examined, in one model. The organism is not treated—absorption, distribution, metabolism and excretion are not the subject. Only dissolution in a vessel is computed. The surface area is held constant—particles shrink as they dissolve, and this model ignores that. The absolute times are approximate; the ratios are the robust part. The Ostwald–Freundlich effect is not treated—for nanoparticles the solubility itself rises slightly, but at $1\ \mu\text{m}$ that correction is not the subject. Polymorphism is not treated—a change of crystal form does move the solubility; this paper mills within one crystal form. Relation to earlier papers: Paper 369 showed that pasteurisation is a dose, not a temperature—there too one phrase named two things. Paper 384 showed that free-space loss is not a loss—here “poor solubility” is not solubility. Paper 300 showed that same-root and different-root can be decided—solubility and dissolution rate are different-root by that criterion. Paper 362 showed that lifting the stones is not the bottleneck—here the solubility is not the bottleneck. What is added is putting numbers on area, count and time at four particle sizes, showing that the area changes by exactly 1000, tracking the time to 90 per cent from 49.34 hours to 2.96 minutes, confirming that the count changes by exactly 1000 per decade of size, and placing the separator at “equilibrium amount or arrival time”.

1. Notation and the Question

Setting: divide a mass m of a substance of density ρ evenly into spheres of diameter d .

$$A = \frac{6m}{\rho d}, \quad N = \frac{6m}{\rho \pi d^3}$$

Let dissolution follow the Noyes–Whitney equation.

$$\frac{dC}{dt} = \frac{DA}{hV}(C_s - C)$$

D is the diffusion coefficient, h the boundary-layer thickness, V the volume of medium, C_s the solubility.

Observation 1.1

C_s appears only inside the bracket. The prefactor of the rate is $DA/(hV)$ — C_s decides how far it goes and does not enter how fast.

Observation 1.2

A moves with particle size. At the same mass, finer means more— C_s does not move with particle size.

Observation 1.3

so the two can be moved independently. Milling touches only A —that independence is what the numbers show.

Question: when we say “poorly soluble”, what is it that is small?

2. The Area Grows a Thousandfold and the Count a Billionfold

Computation 2.1: surface area and particle count for $\rho = 1200 \text{ kg/m}^3$ and $m = 100 \text{ mg}$ (computed in this paper).

Size d	Area $A \text{ [m}^2\text{]}$	Count N
1000 μm	5.000000×10^{-4}	1.591549×10^2
100 μm	5.000000×10^{-3}	1.591549×10^5
10 μm	5.000000×10^{-2}	1.591549×10^8
1 μm	5.000000×10^{-1}	1.591549×10^{11}

Observation 2.2

the area changes by exactly 1000 from top to bottom. From 5.0×10^{-4} to $5.0 \times 10^{-1} \text{ m}^2$ — $A \propto 1/d$, so a thousandth of the size is a thousand times the area.

Observation 2.3

the count changes by exactly 1000 per decade of size. From 159 to 1.59×10^{11} — $N \propto 1/d^3$.

Observation 2.4

100 mg of powder carries 0.5 m^2 of surface. About eight sheets of A4—at one tenth of a gram.

Observation 2.5

every row is the same substance in the same amount. Nothing has changed chemically—only the way it is divided.

3. Forty-Nine Hours Becomes Three Minutes, and the Solubility Has Not Moved

Computation 3.1: dissolution for $D = 7 \times 10^{-10} \text{ m}^2/\text{s}$, $h = 30 \text{ }\mu\text{m}$, $V = 900 \text{ mL}$ (computed in this paper).

Size d	Time constant τ [s]	Time to 90 %	Solubility C_s
1000 μm	77142.86	49.34 hours	unchanged
100 μm	7714.29	4.93 hours	unchanged
10 μm	771.43	29.60 minutes	unchanged
1 μm	77.14	2.96 minutes	unchanged

Observation 3.2

this is the core of the paper. The last column reads “unchanged” in all four rows—the time to 90 per cent moves by a factor of a thousand, from 49.34 hours to 2.96 minutes, and the solubility does not move at all.

Observation 3.3

the final endpoint is also the same in all four rows. Wait long enough and the same amount dissolves—only the waiting differs.

Observation 3.4

49.34 hours is, in practice, “does not dissolve”. Longer than gastrointestinal transit——2.96 minutes is “dissolves at once”. The same drug becomes both, by way of a mill.

Observation 3.5

$\ln 10 = 2.302585$ is common to all four rows. $t_{90} = \tau \ln 10$ ——the shape is identical and only the scale differs.

Observation 3.6

the shape is that of Paper 362. There lifting the stones was not the bottleneck——here the solubility is not the bottleneck. In both, the thing that carries the name is not the thing that acts.

4. A Mill Does Not Touch Thermodynamics

Observation 4.1

C_s is set by substance, solvent and temperature. A thermodynamic equilibrium amount——particle size does not enter its definition.

Observation 4.2

A is set by shape. A geometric quantity——what the substance is enters $A = 6m/(\rho d)$ only as the density.

Observation 4.3

they are different-root by the criterion of Paper 300. One is set by thermodynamics, the other by geometry——one phrase, “poorly soluble”, names two things with different roots.

Observation 4.4

which one is at fault decides the tool. For solubility: make a salt, change the crystal form, use a solubiliser
——for speed: mill. Misdiagnose and you pick a tool that cannot work.

Observation 4.5

at the extreme, however, they mix. For nanoparticles the Ostwald–Freundlich effect raises the solubility
itself——small at 1 μm , not negligible at 100 nm. The separator breaks if the size is pushed down too far.

5. Separator: Equilibrium Amount, or Arrival Time

Observation 5.1

separator——does it fail to dissolve even given time, or does it dissolve given time but not in time.

What is small	Set by	Moves on milling	Remedy
Solubility C_s	thermodynamics	does not move	salt, polymorph, solubiliser
Dissolution rate	geometry (A)	moves 1000×	milling

Observation 5.2

the third column is the test. Does the dissolution curve move when the sample is milled——if it does not, the
bottleneck is the solubility.

Observation 5.3

this separator can be run as an experiment. Mill the same sample and measure——the result falls into one of
two cases.

Observation 5.4

the separator can be moved. Increase the medium until sink conditions hold and the ceiling set by solubility disappears——what remains is speed alone.

Observation 5.5

to be honest——both 49.34 hours and 2.96 minutes come from a model holding the area constant. Particles do shrink as they dissolve, so the late stage is slower——what does not move is that the ratio is exactly 1000 and that C_s is the same in all four rows.

Observation 5.6

one last thing——“poorly soluble” folds a statement about amount and a statement about time into one word. Folded, it hides which tool to reach for——one question unfolds it: what happens if you wait long enough.

6. Roll Call and Closing

1. $A = 6m/(\rho d)$ (Section 1): **inversely proportional to size.**
2. 5.0×10^{-4} to $5.0 \times 10^{-1} \text{ m}^2$ (Computation 2.1): **exactly 1000 times.**
3. 159 to 1.591549×10^{11} particles (Computation 2.1): **1000 per decade of size.**
4. 100 mg carries 0.5 m^2 (Observation 2.4): **about eight sheets of A4.**
5. 90 % in 49.34 hours or 2.96 minutes (Computation 3.1): **a factor of 1000.**
6. Solubility unchanged in all four rows (Observation 3.2): **it does not move at all.**
7. The endpoint is also the same (Observation 3.3): **only the waiting differs.**
8. $t_{90} = \tau \ln 10$ (Observation 3.5): **$\ln 10 = 2.302585$ throughout.**
9. Different-root (Observation 4.3): **thermodynamics and geometry.**
10. They mix in the nanometre range (Observation 4.5): **the separator breaks if pushed too far.**

Closing: when a drug is called “poorly soluble”, two different quantities are being called by one name——how much dissolves, and how long it takes to get there. In the Noyes–Whitney equation the solubility C_s appears only inside the bracket—— $dC/dt = DA/(hV)(C_s - C)$, so C_s decides how far it goes and does not enter how fast. The prefactor is

$DA/(hV)$, and the only part of it that moves with particle size is A . At fixed mass the area is $A = 6m/(\rho d)$, inversely proportional to size—taking 100 mg of a substance of density 1200 kg/m³ from 1 mm to 1 μ m raises the area from 5.0×10^{-4} to 5.0×10^{-1} m², exactly 1000 times, and takes the count from 159 to 1.591549×10^{11} , exactly 1000 per decade of size. One hundred milligrams of powder then carries about eight sheets of A4 in surface. Every row is the same substance in the same amount; only the way it is divided has changed. And the time to 90 per cent falls from 49.34 hours to 2.96 minutes—a factor of a thousand. Yet the solubility does not move at all across the four sizes, and given enough time the final endpoint is identical. Only the waiting differs. Forty-nine hours is longer than gastrointestinal transit and so is, in practice, “does not dissolve”; three minutes is “dissolves at once”—the same drug becomes both, by way of a mill. A mill does not touch thermodynamics— C_s is an equilibrium amount set by substance, solvent and temperature, and particle size does not enter its definition. A is geometric, and what the substance is enters only as the density. They are different-root by the criterion of Paper 300, and one phrase names two things with different roots. As in Paper 362, where lifting the stones was not the bottleneck, the thing that carries the name is not the thing that acts. One thing does the separating—does it fail to dissolve even given time, or does it dissolve given time but not in time. The test is whether the dissolution curve moves when the sample is milled; if it does not, the bottleneck is the solubility. Which one is at fault decides the tool—salt, polymorph or solubiliser for solubility, milling for speed. Misdiagnose and you pick a tool that cannot work. To be honest—both 49.34 hours and 2.96 minutes come from a model holding the area constant, and particles do shrink as they dissolve, so the late stage is slower. What does not move is that the ratio is exactly 1000 and that C_s is the same in all four rows. The separator also breaks if the size is pushed down too far—in the nanometre range the Ostwald–Freundlich effect raises the solubility itself. One last thing—“poorly soluble” folds a statement about amount and a statement about time into one word. Folded, it hides which tool to reach for. One question unfolds it: what happens if you wait long enough.

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Yuuki YAMAGISHI (山岸 勇輝)

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