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Chapter 6

Solubility

To future healthcare professionals, At the heart of your future medical practice lies a universal language, that of **chemical equilibria**. This chapter reveals how these fundamental principles govern the physiological and pathological processes you will encounter daily.
For the future physician, understanding solubility equilibria sheds light on the formation of kidney stones. You will learn to decipher crystallogenesis and master dissolution strategies that transform the therapeutic approach to urinary calculi.(41)
For the future pharmacist, these concepts become tools for optimizing pharmaceutical formulation. Mastery of solubility parameters and acid-base equilibria will enable you to design formulations ensuring maximal bioavailability of active ingredients.
For the future dentist, precipitation-dissolution equilibria reveal the intimate mechanisms of dental demineralization.(42) This knowledge underpins preventive approaches and enamel remineralization strategies.
For the future biologist, modeling ionic equilibria in biological media opens the way to precise diagnosis and understanding of metabolic disorders.
More than a chemistry chapter, this is your future clinical toolkit, the essential bridge between fundamental sciences and your professional practice. Each mastered equilibrium becomes a refined diagnosis, each understood constant transforms into an optimized therapeutic strategy.

From equilibrium constant to observable phenomenon:

In chemistry, most phenomena take place in the invisible molecular theater, at scales where human intuition struggles to project itself. Yet solubility represents a remarkable exception: it is the moment when the abstract becomes tangible, when thermodynamic equations materialize into observable phenomena. When a solute reaches its dissolution limits in a solvent, the invisible suddenly becomes visible: a crystalline precipitate appears, a solution turns cloudy, a pathology emerges.
The Clinical Breaking Point:
This precipitation moment is not just a laboratory curiosity; it is often the starting point of a pathological cascade:

- A kidney stone that obstructs the urinary tract
- A drug that precipitates in tissues
- A crystalline deposit that inflames joints
- Dental enamel that dissolves under acid attack

For you, future healthcare professionals, understanding solubility transcends theoretical exercise. It is the acquisition of a **fundamental diagnostic language** that will enable you to interpret biological analyses, understand drug mechanisms of action at the molecular level, and identify the origin of pathologies linked to dissolution imbalances.
Challenges of integrating fundamental sciences into clinical practice:
The main epistemological challenge for the health sciences student lies in establishing the conceptual bridge between an abstract thermodynamic constant, the solubility product K_s, and its tangible clinical manifestations.

Table 6.1 Correspondence between solubility concepts and clinical manifestations

Chemical Concept	Clinical Manifestation
Solubility product $\mathbf{K_s}$	Threshold for kidney stone formation
Molar solubility **s**	Maximum absorbable drug concentration
Ionic product **Q**	Risk of pathological precipitation
Common ion effect	Dental prevention strategy via fluoridation
pH influence	Modulation of drug bioavailability

The pedagogical challenge is to demonstrate that this seemingly arid mathematical constant, K_s, governs biological phenomena of remarkable complexity. Our goal is to make this link intuitive, establishing that mastery of solubility principles constitutes one of the fundamental pillars of enlightened medical practice.

6.1 Solubility, Pillar of Modern Pharmacology:

Solubility constitutes a determining physicochemical parameter in the journey of active ingredients through the body. This fundamental property conditions the bioavailability of therapeutic molecules, where a biologically active but insoluble compound cannot reach its physiological sites of action. Solubility equilibria thus govern the absorption, distribution, and clinical efficacy of pharmacological agents.
Solubility directly influences two crucial pharmacokinetic parameters:

- **Bioavailability**: fraction of the administered dose reaching systemic circulation
- **Pharmacokinetics**: temporal profile of plasma concentration

A drug with low solubility invariably exhibits erratic absorption, leading to suboptimal therapeutic efficacy and an unpredictable adverse effect profile. In parallel, numerous pathological entities — kidney stones, gout, cholelithiasis — essentially arise from solubility disorders.

Mapping of Fundamental Clinical Applications

To grasp the systemic scope of this concept, let us examine the four areas of clinical application where solubility plays a determining role:

a) **Biomolecular Diagnosis**

> Solubility constitutes the physicochemical foundation of many biological tests. The measurement of urinary concentrations of calcium, oxalate, phosphate, or uric acid provides direct prognostic indicators of an individual's propensity to form stones.[41] When the ionic product $[Ca^{2+}][C_2O_4{}^{2-}]$ in urine exceeds the solubility product K_s of calcium oxalate, crystal nucleation becomes thermodynamically inevitable.

b) **Pharmaceutical Engineering**

> Nearly all therapeutic agents are administered as solid (tablets, capsules) or liquid pharmaceutical forms. Mastery of dissolution parameters represents a major technological challenge for the pharmaceutical industry, aiming to guarantee reproducible bioavailability and optimal dosage. Size reduction techniques (micronization, microfluidization),[43] salt formation, and the use of co-solvents are specifically designed to modulate solubility.

c) **Environmental Toxicology**

> Xenobiotic bioaccumulation represents a global health challenge. Persistent pollutants, particularly heavy metals (mercury, lead, cadmium) and persistent organic pollutants (POPs), have minimal aqueous solubility but marked lipid affinity. This solubility dichotomy leads to their progressive accumulation along trophic chains, transforming an invisible molecular phenomenon into a tangible epidemiological threat.[44]

d) **Advanced Medical Imaging**

> Contrast agents used in medical imaging (CT scan, radiography, MRI) judiciously exploit solubility properties. Some products must exhibit **controlled** solubility: sufficient to allow administration, but not to the point of eliminating the contrast effect. In digestive radiology, barium salt suspensions perfectly illustrate this logic: their low solubility limits systemic absorption while ensuring strong opacification of the structures under examination.[45]

Mastering solubility is not limited to learning thermodynamic equations. It is acquiring the key to reading a

fundamental mechanism governing biological homeostasis, clinical pharmacology, and molecular pathophysiology. Your understanding of these principles will become the basis for informed medical decisions.

The Meeting of Two Worlds: Solid and Solution

- **The silent dialogue of ions**
  - **Scenario 1: Dissolution (Release process)**
    Dissolution represents the process by which an ionic solid, such as sodium chloride (NaCl), releases its constituent ions into water. Under the action of polar water molecules, ions are pulled from the crystal structure and surrounded by a solvation sphere. This process can be represented by the equation:

$$\mathrm{NaCl_{(s)}} \xrightarrow{\text{dissolution}} \mathrm{Na^{+}_{(aq)}} + \mathrm{Cl^{-}_{(aq)}}$$

    The energy required to break the crystal lattice is compensated by the energy gained during ion solvation, making the overall process favorable in many cases.
  - **Scenario 2: Precipitation (Formation process)**
    Conversely, precipitation describes the process of forming a solid from ions in solution. When the ion concentration exceeds a certain threshold, called the solubility product, ions reassemble to form a stable crystal lattice. This phenomenon is expressed by:

$$\mathrm{Na^{+}_{(aq)}} + \mathrm{Cl^{-}_{(aq)}} \xrightarrow{\text{precipitation}} \mathrm{NaCl_{(s)}}$$

    Precipitation is favored when the ionic product exceeds the solubility constant K_s, indicating that the solution is supersaturated.
- **Dynamic Equilibrium: The Negotiated Peace**
  - **Mathematical representation of equilibrium**
    The dynamic equilibrium between dissolution and precipitation is quantified by the solubility product K_s. For a generic salt $\mathrm{M}_a\mathrm{X}_b$, the equilibrium relationship is written:

$$\mathrm{M}_a\mathrm{X}_{b(\mathrm{s})} \rightleftharpoons \mathrm{aM^{b+}_{(aq)}} + \mathrm{bX^{a-}_{(aq)}}$$

$$K_s = [\mathrm{M}^{b+}]^a \cdot [\mathrm{X}^{a-}]^b$$

    This constant represents, in the usual approximation of dilute solutions, the product of the **concentrations** of ions at equilibrium, each raised to the power of its stoichiometric coefficient. **Note:** in thermodynamic rigor, the exact expression uses **activities** a_i; in dilute solution, one often approximates $a_i \approx [i]$, but in concentrated media (physiological media) this approximation may become limited.[(31)]
  - **Concert hall analogy**
    Imagine a concert hall with spectators constantly entering and leaving. Although individuals change, the total number of people in the hall remains constant. Similarly, in a system at equilibrium:
    * Ions constantly leave the crystal (dissolution)
    * Other ions simultaneously deposit (precipitation)
    * The rates of both processes are equal
    * The concentration of species in solution remains unchanged

    This equilibrium is not static but dynamic, with continuous exchange between the solid and aqueous phases, maintained by the equality of the rates of opposite reactions.

Key point: Solubility equilibrium represents a compromise between two opposing forces — the tendency to dissolve and the tendency to precipitate — which perfectly cancel at the macroscopic level while remaining active at the molecular level.

6.2 The Solubility Product "K_s":

The Solubility Product (K_s) (Your Compass in the Invisible) represents the equilibrium constant that governs the dissolution of sparingly soluble compounds. It allows us to quantify the invisible and predict the behavior of salts in solution, serving as a valuable guide in the analysis of heterogeneous systems.

- **The Constant That Reveals Secrets**

▷ **Formal definition of the Solubility Product**

The Solubility Product (K_s) is defined as the equilibrium constant associated with the dissolution of a sparingly soluble ionic compound in water.[30] It represents the product of the molar concentrations of ions in solution, each raised to the power of its stoichiometric coefficient in the dissolution equation, when the solution is saturated and in equilibrium with the solid.

Unlike classical equilibrium constants, K_s does not include the concentration of the solid, as it is considered constant in the equilibrium constant expression.

▷ **General mathematical expression**

For a generic ionic compound of formula M_aX_b, where a and b are the stoichiometric coefficients,[31] the dissolution is written:

$$M_aX_b(s) \rightleftharpoons a\,M^{b+}(aq) + b\,X^{a-}(aq)$$

Note: in rigor, the solubility product is expressed using activities a_i. In dilute solution, one often approximates $a_i \approx [i]$. (where a and b are the stoichiometric coefficients, chosen to ensure electroneutrality).

General expression:

$$K_s = a\left(M^{b+}\right)^a\ a(X^{a-})^b\ \approx\ [M^{b+}]^a\,[X^{a-}]^b$$

Concrete examples: Silver chloride:[46]

$$AgCl(s) \rightleftharpoons Ag^+(aq) + Cl^-(aq) \quad K_s = [Ag^+]\,[Cl^-] = 1.8 \times 10^{-10}$$

Calcium sulfate:[46]

$$CaSO_4(s) \rightleftharpoons Ca^{2+}(aq) + {SO_4}^{2-}(aq) \quad K_s = [Ca^{2+}]\,[{SO_4}^{2-}] = 2.4 \times 10^{-5}$$

Iron(III) hydroxide:[46]

$$Fe(OH)_3(s) \rightleftharpoons Fe^{3+}(aq) + 3\,OH^-(aq) \quad K_s = [Fe^{3+}]\,[OH^-]^3 = 2.8 \times 10^{-39}$$

▷ **Orders of magnitude (indicative classification)**

▷ **Highly soluble salts** In this case, the solid dissolves almost completely: one generally does not work with a solubility product K_s to predict precipitation. They are treated as dissociated electrolytes (e.g. NaCl, KNO_3, $AgNO_3$).

▷ **Sparingly soluble salts (typical case for K_s)** The solubility product K_s is especially useful for sparingly soluble solids, as it serves as the saturation/precipitation threshold via comparison of Q and K_s. **Caution:** direct comparison of K_s values is only meaningful for comparable stoichiometries (MX and MX, etc.).

Examples (at given T):

- AgCl: $K_s = 1.8 \times 10^{-10}$
- $CaSO_4$: $K_s = 2.4 \times 10^{-5}$
- $BaSO_4$: $K_s \approx 1.1 \times 10^{-10}$

▷ **Very sparingly soluble salts (almost insoluble)** These solids have extremely low K_s values: their dissolution is negligible at the macroscopic scale, but measurable and exploitable in analytical chemistry.

Examples (at given T):

- $Fe(OH)_3$: $K_s = 2.8 \times 10^{-39}$
- HgS: $K_s = 4 \times 10^{-53}$
- Ag_2S: $K_s = 6.3 \times 10^{-50}$

▷ **Concrete Case: The Mystery of Kidney Stones**

▷ **Medical case study** Kidney stones (renal lithiasis) are often composed of calcium oxalate CaC_2O_4. This sparingly soluble salt can precipitate in the urinary tract when urine becomes supersaturated.

Data (order of magnitude):

- $K_s(CaC_2O_4) = 2.3 \times 10^{-9}$ (tabulated value at 25 °C; at 37 °C, the order of magnitude remains $\sim 10^{-9}$).
- **Free** Ca^{2+} concentration in urine: $2.5 \times 10^{-3}\,mol\,L^{-1}$

· **Free** oxalate $C_2O_4^{2-}$ concentration: $5.0 \times 10^{-5}\,\text{mol}\,\text{L}^{-1}$

▷ **Application of Q to K_s**

To predict whether precipitation occurs, we calculate the ionic product Q and compare it to K_s:

$$Q = [Ca^{2+}][C_2O_4^{2-}] = (2.5 \times 10^{-3}) \times (5.0 \times 10^{-5}) = 1.25 \times 10^{-7}$$

Analysis:

* $Q = 1.25 \times 10^{-7}$
* $K_s = 2.3 \times 10^{-9}$
* $Q > K_s$: the solution is supersaturated, precipitation is thermodynamically favored

Medical interpretation: The risk of kidney stone formation is high under these conditions. Preventive strategies include:

* Increasing hydration to dilute ions
* Reducing dietary oxalate intake
* Controlling calcium concentration
* Maintaining $Q < K_s$ to avoid precipitation

This case illustrates how K_s enables understanding and prevention of a concrete health problem.

In summary: K_s is much more than a simple constant; it is a powerful predictive tool that guides us in understanding dissolution and precipitation phenomena, with applications ranging from the chemical industry to clinical medicine.

Definition

Fundamental difference between Q and K_s:

Ionic Product (Q)	**Solubility Product** (K_s)
Instantaneous value	**Equilibrium value**
Describes any state of the system	Describes the equilibrium state only
Can take any value ≥ 0	Constant value at given temperature
Varies over time	**Thermodynamic constant**
Depends on initial concentrations	Intrinsic property of the compound
Prediction tool	Comparison reference

Table 6.2 Detailed comparison between Q and K_s

Ionic Product (Q) and Solubility Product (K_s)	
Ionic Product Q	**Solubility Product K_s**
Definition: Instantaneous value of the product of concentrations	**Definition:** Constant value at saturation equilibrium
Expression: $Q = [M^{b+}]^a_{\text{actual}} \cdot [X^{a-}]^b_{\text{actual}}$	**Expression:** $K_s = [M^{b+}]^a_{\text{eq}} \cdot [X^{a-}]^b_{\text{eq}}$
Variability: Can take any value ≥ 0	**Variability:** Constant at given temperature
Utility: Prediction and diagnostic tool	**Utility:** Thermodynamic reference
Analogy: A patient's current temperature	**Analogy:** Normal body temperature (37°C)

Clinical case

Clinical decision tree based on Q/K_s:

- **$Q < 0.8K_s$** : **Safety zone** - No immediate risk
- **$0.8K_s < Q < K_s$** : **Watchful zone** - Monitoring required
- **$Q > K_s$** : **Danger zone** - Precipitation possible
- **$Q > 2K_s$** : **Critical zone** - Precipitation imminent

Important

Important thermodynamic note:

- In **thermodynamic rigor**, the solubility product is expressed using **activities**:

$$K_s = a(\mathrm{M}^{b+})^a \cdot a(\mathrm{X}^{a-})^b$$

  where $a_i = \gamma_i[i]$ with γ_i the activity coefficient.
- In **dilute solution** ($\gamma_i \approx 1$), one often uses the approximation:

$$K_s \approx [\mathrm{M}^{b+}]^a \cdot [\mathrm{X}^{a-}]^b$$

- In **biological media** (urine, plasma), often concentrated, this approximation may be limited.

6.3 Molar Solubility:

6.3.1 Definition and Advanced Experimental Methodology

Thermodynamic definition: Molar solubility (s) is the equilibrium concentration of an ionic solid in its saturated solution, corresponding to the state where the rates of dissolution and precipitation are equal. It represents the boundary between the metastable and unstable domains of the system.
Experimental methods: The determination of **molar solubility** s of an ionic solid can be performed using various high-precision instrumental techniques. Each method allows direct or indirect access to the concentration of dissolved ions at saturation equilibrium.

- **Precision Conductimetry:** This method is based on measuring the conductivity of the saturated solution. For a sparingly soluble electrolyte, the molar conductivity Λ_m varies according to **Kohlrausch's** law:

$$\Lambda_m = \Lambda_m^0 - A\sqrt{c}$$

  Extrapolation to infinite dilution allows obtaining Λ_m^0, then the concentration of dissolved ions $c = s$. Thus, conductimetry allows indirect determination of molar solubility from the electrical properties of the solution.
- **UV-Visible Spectrophotometry:** If one of the ions from dissolution absorbs in the UV or visible range, the Beer-Lambert law applies:

$$A = \varepsilon\, l\, c$$

  where A is the absorbance, ε the molar extinction coefficient, and l the cell path length. From a calibration curve ($A = f(c)$), the concentration at saturation is determined, equal to the molar solubility s.
- **Advanced Potentiometry:** The use of ion-selective electrodes allows measuring the potential of a saturated solution for a given ion. The potential obeys the Nernst equation:

$$E = E^0 + \frac{RT}{zF} \ln a_i$$

  where a_i is the activity of the ion. The measurement of E thus leads to the determination of a_i, then the ionic concentration, i.e., the **molar solubility** s.
- **ICP-MS (Inductively Coupled Plasma Mass Spectrometry):** This ultra-sensitive technique allows the determination of elements at trace levels (down to ppb). The measured concentration of the dissolved cation directly corresponds to the **molar solubility** of the solid at equilibrium.
- **Microcalorimetry:** Microcalorimetry measures the heat absorbed or released during the dissolution of the solid. This method allows direct determination of the enthalpy of dissolution $\Delta H_{\text{dissolution}}$. Although it does not directly give s, it allows studying the influence of temperature on solubility via the Van't Hoff equation:

$$\frac{d(\ln s)}{dT} = \frac{\Delta H_{\text{dissolution}}}{RT^2}$$

6.4 Relationships between "K_s" and "s":

▷ **Fundamental Principle: The Stoichiometric Symphony**
The relationship between the solubility product K_s and molar solubility s is based on a universal principle: **the stoichiometry of dissolution determines the mathematical power that relates them**. This

relationship is not arbitrary but emerges directly from the coefficients of the balanced chemical equation.

▷ **The General Law: A Universal Equation**

For any ionic compound of formula M_aX_b dissolving according to:

$$\underset{}{M_aX_{b(s)}} \rightleftharpoons \underset{[M^{b+}] = (a \cdot s)}{aM^{b+}_{(aq)}} + \underset{[X^{a-}] = (b \cdot s)}{bX^{a-}_{(aq)}}$$

$$\begin{aligned} K_s &= [M^{b+}]^a \cdot [X^{a-}]^b \\ &= (a \cdot s)^a \cdot (b \cdot s)^b \\ &= a^a \cdot s^a \cdot b^b \cdot s^b \\ &= a^a \ b^b \ s^{a+b} \end{aligned}$$

The fundamental relationship is established as follows:

Key takeaways

$$\text{Solubility product :} \quad K_s = a^a b^b s^{a+b} \tag{6.1}$$

$$\text{Molar solubility :} \quad s = \sqrt[a+b]{\frac{K_s}{a^a b^b}} \tag{6.2}$$

▷ **Conceptual Explanation: Why this Form?**

The presence of the terms a^a and b^b in the relationship may be surprising, but it is explained by:

- **Raising to a power**: Each ionic concentration is raised to the power of its stoichiometric coefficient in the K_s expression
- **Multiplication**: Concentrations are multiplied together in the solubility product expression
- **Combination**: These two mathematical operations naturally lead to a^a and b^b

▷ **Systematic Resolution Approach**

a) **Identify** the compound formula and determine a and b
b) **Write** the balanced dissolution equation
c) **Establish** the link between ionic concentrations and solubility s
d) **Substitute** into the K_s expression
e) **Solve** the equation for s

▷ **Validation by Dimensional Analysis**

Dimensional consistency confirms the validity of the relationship: For a salt A_aB_b of solubility s:

$$K_s = (as)^a (bs)^b = a^a b^b s^{a+b}$$

$$s^{a+b} = \frac{K_s}{a^a b^b} \quad \Rightarrow \quad s = \left(\frac{K_s}{a^a b^b}\right)^{\frac{1}{a+b}}$$

Dimensional analysis:

$$\begin{aligned} [K_s] &= (\text{mol} \cdot \text{L}^{-1})^{a+b} \\ \left[\frac{K_s}{a^a b^b}\right] &= (\text{mol} \cdot \text{L}^{-1})^{a+b} \quad \text{(since } a^a b^b \text{ is dimensionless)} \\ \left[\left(\frac{K_s}{a^a b^b}\right)^{\frac{1}{a+b}}\right] &= \text{mol} \cdot \text{L}^{-1} \quad \text{consistent with the dimension of } s \end{aligned}$$

▷ **Case of MX Type Salts (a:b = 1:1) also called Symmetric Equilibrium**

$$\underset{}{MX_{(s)}} \rightleftharpoons \underset{[M^+] = s}{M^+_{(aq)}} + \underset{[X^-] = s}{X^-_{(aq)}}$$

$$K_s = [M^+][X^-] = s \times s = s^2 \Rightarrow s = \sqrt{K_s}$$

Detailed clinical examples:

– **Silver chloride AgCl** (with $K_s = 1.77 \times 10^{-10}$): used in antisepsis and wound dressings. AgCl is an insoluble compound used for its antibacterial properties in medical devices. It is a white crystalline powder, incorporated into dressings or ointments.[47]
AgCl acts through controlled release of silver ions: which are slowly released in low concentration at the wound surface, thus disrupting the vital functions of bacteria and fungi, ensuring prolonged antiseptic action without systemic toxicity.

$$\underset{}{\mathrm{AgCl}_{(s)}} \rightleftharpoons \underset{[\mathrm{Ag}^+] = s}{\mathrm{Ag}_{(aq)}{}^{+}} + \underset{[\mathrm{Cl}^-] = s}{\mathrm{Cl}^-{}_{(aq)}}$$

$$s = \sqrt{1.77 \times 10^{-10}} = 1.33 \times 10^{-5}\ \mathrm{mol \cdot L^{-1}}$$

$$\text{equivalent mass concentration} = 1.33 \times 10^{-5} \times 143.32 = 1.91\ \mathrm{mg \cdot L^{-1}}$$

This infinitesimal concentration (less than 2 mg/L) perfectly explains why AgCl is safe while being effective as an antiseptic (remember that an antiseptic is a "disinfectant adapted to the human body" powerful enough to kill microbes, but gentle enough not to damage healthy tissues).

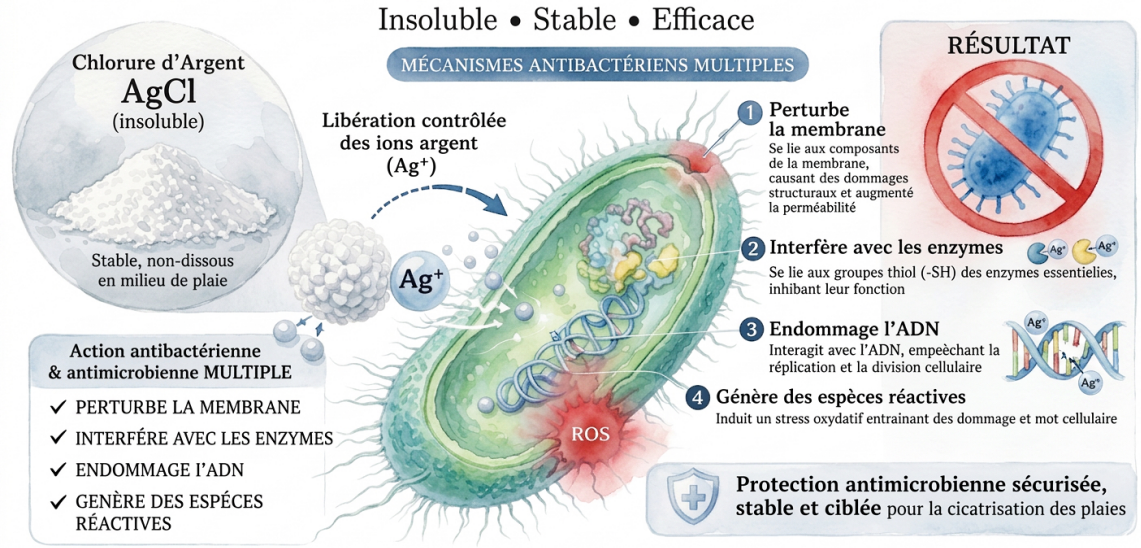

Figure 6.1 The multiple therapeutic properties of silver dressings used in wound healing

– **Barium sulfate $\mathbf{BaSO_4}$** (with $K_s = 1.08 \times 10^{-10}$): Radiological contrast agent. $BaSO_4$ is a radio-opaque contrast agent used primarily in digestive radiology. It is a white insoluble powder mixed with water to form a liquid suspension.[45] $BaSO_4$ acts through its high atomic density: It absorbs X-rays much better than surrounding soft tissues, Creates a white contrast on radiographs, and Molds the digestive walls to reveal their morphology.

$$\underset{}{\mathrm{BaSO}_{4(s)}} \rightleftharpoons \underset{[\mathrm{Ba}^{2+}] = s}{\mathrm{Ba}^{2+}_{(aq)}} + \underset{[\mathrm{SO_4}^{2-}] = s}{\mathrm{SO_4}^{2-}{}_{(aq)}}$$

$$s = \sqrt{1.08 \times 10^{-10}} = 1.04 \times 10^{-5}\ \mathrm{mol \cdot L^{-1}}$$

This extreme insolubility is the key to safety, characterized by: No systemic toxicity, $BaSO_4$ practically does not pass into the blood, 100% elimination of the ingested dose (eliminated in feces), in addition to no drug interactions and unchanged in the body.

▷ **Case of 1:2 Salts (Type $\mathbf{MX_2}$), Asymmetric Dissolution:**
Advanced Stoichiometric Analysis,

$$\underset{}{\mathrm{MX}_{2(s)}} \rightleftharpoons \underset{[\mathrm{M}^{2+}] = s}{\mathrm{M}^{2+}_{(aq)}} + \underset{[\mathrm{X}^-] = 2s}{2\,\mathrm{X}^-_{(aq)}}$$

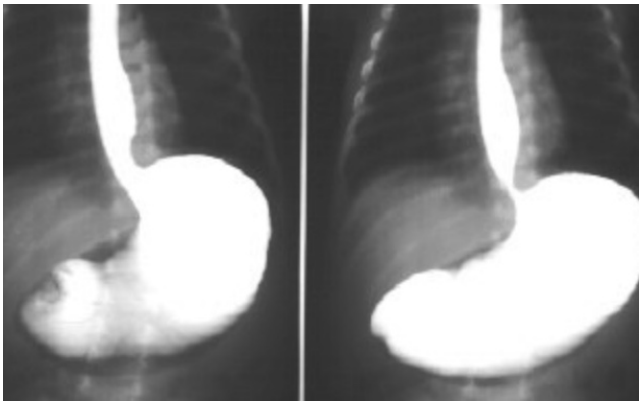

Figure 6.2 Digestive Radiological Examinations TOGD (Transit Œso-Gastro-Duodénal).

Figure 6.3 EZ-HD®: High density barium

$$K_s = [M^{2+}][X^-]^2 = s \times (2s)^2 = 4s^3 \Rightarrow s = \sqrt[3]{\frac{K_s}{4}}$$

Generally speaking: For a salt (see equation: (6.1)):

$$\mathrm{M}_a\mathrm{X}_b : \mathrm{K}_s = (a^a)(b^b)s^{a+b}$$
$$\mathrm{MX}_2 : a = 1,\ b = 2 \Rightarrow K_s = 1^1 \cdot 2^2 \cdot s^3 = 4s^3$$

Complete clinical examples:

– **Calcium fluoride $\mathbf{CaF_2}$** (with $K_s = 3.45 \times 10^{-11}$): "Caries prevention" CaF_2 is an insoluble deposit that forms on enamel after fluoride application. It constitutes a slow-release fluoride reservoir.[42]
CaF_2 protects teeth through a dual mechanism: It releases F^- ions during acid attacks, Promotes remineralization of dental enamel, and Inhibits the metabolism of cariogenic bacteria.

$$\underset{}{\mathrm{CaF}_{2(s)}} \rightleftharpoons \underset{[\mathrm{Ca}^{2+}] = s}{\mathrm{Ca}^{2+}_{(aq)}} + \underset{[\mathrm{F}^-] = 2s}{2\,\mathrm{F}^-_{(aq)}}$$

$$K_s = [\mathrm{Ca}^{2+}][\mathrm{F}^-]^2 = s \times (2s)^2 = 4s^3$$
$$s = \sqrt[3]{\frac{K_s}{4}} = \sqrt[3]{\frac{3.45 \times 10^{-11}}{4}} = 2.05 \times 10^{-4}\ \mathrm{mol \cdot L^{-1}}$$
$$[\mathrm{F}^-] = 2s = 4.10 \times 10^{-4}\ \mathrm{mol \cdot L^{-1}}$$
$$\text{Optimal concentration} : 0.7 - 1.2\ \text{ppm} = (3.7 - 6.3) \times 10^{-5}\ \mathrm{mol \cdot L^{-1}}$$

This optimal solubility allows CaF_2 to play its therapeutic role perfectly: Sufficient fluoride release to remineralize enamel, Stability in the mouth between meals, Safety through absence of systemic absorption, and Prolonged effect reducing application frequency. Concrete examples include fluoridated toothpastes (Signal Caries protection, Parodentax fluor, Elmex, etc.), Fluoride varnishes applied in dental offices, and mouthwashes.

∗ **Silver chromate $\mathbf{Ag_2CrO_4}$** (with $K_s = 1.12 \times 10^{-12}$): Reaction endpoint indicator. This brick-red insoluble compound is used as a visual indicator in precipitation titrations.[46]
Its mechanism of action is based on its selective precipitation: It forms a characteristic red precipitate only after depletion of the ions being titrated, Thus clearly marks the equivalence point by color appearance, And allows reliable detection of the titration endpoint.

$$\underset{}{\mathrm{Ag_2CrO_{4(s)}}} \rightleftharpoons \underset{[\mathrm{Ag}^+] = 2s}{2\,\mathrm{Ag}^+_{(aq)}} + \underset{[\mathrm{CrO_4}^{2-}] = s}{\mathrm{CrO_4}^{2-}{}_{(aq)}}$$

$$K_s = [Ag^+]^2[CrO_4{}^{2-}] = (2s)^2 \times s = 4s^3$$
$$s = \sqrt[3]{\frac{K_s}{4}} = \sqrt[3]{\frac{1.12 \times 10^{-12}}{4}} = 6.54 \times 10^{-5}\ \text{mol} \cdot \text{L}^{-1}$$
$$[Ag^+] = 2s = 1.31 \times 10^{-4}\ \text{mol} \cdot \text{L}^{-1}$$

The calculated value of the silver ion concentration determines the precipitation moment: silver chromate appears only after complete precipitation of halides, ensuring precise indication of the titration endpoint.

▷ **Case of 2:3 Salts (Type M_2X_3 - Stoichiometric Complexity)**
Complex Polynomial Relationships,

$$\underset{}{M_2X_{3(s)}} \quad \rightleftharpoons \quad \underset{[M^{3+}] = 2s}{2\,M^{3+}_{(aq)}} \quad + \quad \underset{[X^{2-}] = 3s}{3\,X^{2-}_{(aq)}}$$

Fundamental equation:

$$K_s = [M^{3+}]^2[X^{2-}]^3 = (2s)^2 \times (3s)^3 = 108s^5 \Rightarrow s = \sqrt[5]{\frac{K_s}{108}}$$

Mathematical generalization:

$$\text{For } M_aX_b : s = \sqrt[a+b]{\frac{K_s}{a^a \cdot b^b}}$$
$$M_2X_3 : s = \sqrt[5]{\frac{K_s}{2^2 \cdot 3^3}} = \sqrt[5]{\frac{K_s}{108}}$$

Specialized clinical examples:

– **Iron(III) sulfide Fe_2S_3** ($K_s = 1 \times 10^{-88}$): Implications in metabolic pathology. This compound of remarkable insolubility forms during disorders of iron and sulfur metabolism, particularly in certain intoxications or hereditary pathologies.[44]

$$\underset{}{Fe_2S_{3(s)}} \quad \rightleftharpoons \quad \underset{[Fe^{3+}] = 2s}{2\,Fe^{3+}_{(aq)}} \quad + \quad \underset{[S^{2-}] = 3s}{3\,S^{2-}_{(aq)}}$$

$$K_s = (2s)^2 \times (3s)^3 = 108s^5$$
$$s = \sqrt[5]{\frac{1 \times 10^{-88}}{108}} \approx 1 \times 10^{-18}\ \text{mol} \cdot \text{L}^{-1}$$

Clinical significance: This extreme insolubility prevents any renal elimination and favors tissue accumulation, potentially leading to insoluble deposits in organs (liver, spleen) and disrupting cellular functions.

– **Aluminum oxide Al_2O_3** (corundum): Material of choice for orthopedic implants. The crystalline form α-Al_2O_3 is preferred for prostheses due to its exceptional bio-inertness and mechanical resistance.[31]

$$\underset{}{Al_2O_{3(s)}} \quad \rightleftharpoons \quad \underset{[Al^{3+}] = 2s}{2\,Al^{3+}_{(aq)}} \quad + \quad \underset{[O^{2-}] = 3s}{3\,O^{2-}_{(aq)}}$$

$$K_s = (2s)^2 \times (3s)^3 = 108s^5$$
$$K_s \approx 10^{-34}, \quad s \approx 10^{-7}\ \text{mol} \cdot \text{L}^{-1}$$

Biomedical advantages: This thermodynamic stability gives the material unlimited lifespan in vivo, absence of toxic aluminum ion release, and excellent tissue tolerance, allowing its use in hip and knee prostheses.

Table 6.3 Summary of relationships between K_s and solubility s[30],[48]

Salt type	Dissolution equation	K_s-s relationship	Clinical example
MX (1:1)	$MX_{(s)} \rightleftharpoons M^{+}_{(aq)} + X^{-}_{(aq)}$	$K_s = s^2$	AgCl (antisepsis)
MX_2 (1:2)	$MX_{2(s)} \rightleftharpoons M^{2+}_{(aq)} + 2\,X^{-}_{(aq)}$	$K_s = 4s^3$	CaF_2 (caries prevention)
M_2X (2:1)	$M_2X_{(s)} \rightleftharpoons 2\,M^{+}_{(aq)} + X^{2-}_{(aq)}$	$K_s = 4s^3$	Ag_2CrO_4 (indicator)
M_2X_3 (2:3)	$M_2X_{3(s)} \rightleftharpoons 2\,M^{3+}_{(aq)} + 3\,X^{2-}_{(aq)}$	$K_s = 108s^5$	Fe_2S_3 (pathology)
M_3X_2 (3:2)	$M_3X_{2(s)} \rightleftharpoons 3\,M^{2+}_{(aq)} + 2\,X^{3-}_{(aq)}$	$K_s = 108s^5$	$Ca_3(PO_4)_2$ (stones)
General formula: $M_aX_{b(s)} \rightleftharpoons aM^{b+}_{(aq)} + bX^{a-}_{(aq)}$ $\boxed{K_s = a^a b^b s^{a+b}}$			

6.4.1 Complete Resolution Methodology: Systemic Approach

▷ **Step 1: Clinical Analysis and Chemical Translation** For healthcare professionals, it is very important to follow a certain protocol to solve a problem, whatever its type. In our case, this example where we will address or highlight solubility, the steps are as follows: **Decision-making process:**

a) **Identification of the clinical problem** (lithiasis, formulation, toxicity)
b) **Search for the involved compound** and its chemical formula
c) **Writing the balanced dissolution equation**
d) **Verification of experimental conditions** (T, pH, ionic strength)

Detailed example: "Calcium phosphate kidney stones $Ca_3(PO_4)_2$"

▷ **Step 2: Establishing Precise Stoichiometric Relationships Construction of the rigorous advancement table:**

Reaction equation	$Ca_3(PO_4)_{2(s)}$ $\rightleftharpoons$	$3\,Ca^{2+}_{(aq)}$ +	$2\,PO_4{}^{3-}_{(aq)}$
Initial state (mol/L)	excess	0	0
Equilibrium (mol/L)	excess	$3s$	$2s$

▷ **Step 3: Expression of K_s as a Function of s:**

$$\begin{aligned} K_s &= [Ca^{2+}]^3[PO_4{}^{3-}]^2 \\ &= (3s)^3 \times (2s)^2 \\ &= 27s^3 \times 4s^2 \\ &= 108s^5 \end{aligned}$$

▷ **Step 4: Numerical Resolution and Clinical Validation Complete resolution with known K_s:**

$$\begin{aligned} K_s(Ca_3(PO_4)_2) &= 2.07 \times 10^{-33} = 108s^5 \\ \Rightarrow s^5 &= \frac{2.07 \times 10^{-33}}{108} = 1.92 \times 10^{-35} \\ \Rightarrow s &= \sqrt[5]{1.92 \times 10^{-35}} \\ &= (1.92 \times 10^{-35})^{0.2} = 1.14 \times 10^{-7}\ \text{mol} \cdot \text{L}^{-1} \end{aligned}$$

Clinical interpretation:

* Very low concentration explains the slow formation of stones
* Very low precipitation threshold justifies preventive measures
* Validity of hydration recommendations

6.4.2 The Ionic Product:

6.4.2.1 Fundamental Definition of the Ionic Product (Q)

Definition: The ionic product Q (reaction quotient) describes the instantaneous state of a system for a dissolution reaction.[31] At saturation equilibrium, we have $Q = K_s$.
General mathematical expression:

$$\mathrm{M}_a\mathrm{X}_{b(\mathrm{s})} \rightleftharpoons \mathrm{a}\mathrm{M}^{b+}_{(\mathrm{aq})} + \mathrm{b}\mathrm{X}^{a-}_{(\mathrm{aq})}$$

$$Q = [\mathrm{M}^{b+}]^a \cdot [\mathrm{X}^{a-}]^b$$

Deep physical significance:

- **Kinetic approach:** Q determines the net direction of the reaction
- **Thermodynamic approach:** Q/K_s indicates the sign of ΔG
- **Statistical approach:** Q reflects the probability of nucleation

6.4.2.2 The Three Prediction Rules: Thermodynamic Foundations

▷ **Option 1: Q $< K_s$ (Unsaturated Solution) - Stability Domain**

$$\Delta_r G = RT\ln\left(\frac{Q}{K_s}\right)$$

$$\text{If } Q < K_s \;\Rightarrow\; \ln\left(\frac{Q}{K_s}\right) < 0$$

$$\Rightarrow\; \Delta_r G < 0 \;\Rightarrow\; \text{dissolution thermodynamically favored}$$

$\Delta_r G > 0$: precipitation is thermodynamically favored, but may be delayed by a nucleation barrier (kinetics).
System behavior:

- Net dissolution of solid if present
- No precipitation even in supercooling
- Guaranteed kinetic stability
- Possibility of adding more solute

▷ **Option 2: Q $= K_s$ (Saturation Equilibrium) - Limit State**

$$\Delta G = RT\ln\left(\frac{Q}{K_s}\right) = RT\ln(1) = 0 \Rightarrow \text{System at equilibrium}$$

Dynamic behavior:

- Dissolution rate = Precipitation rate
- Macroscopically constant concentrations
- Continuous molecular exchange at the microscopic level
- Metastable state: any perturbation breaks the equilibrium

Advanced clinical example: Urine saturated with $\mathrm{CaC_2O_4}$

$$[\mathrm{Ca}^{2+}] = 1.52 \times 10^{-4}\ \mathrm{M} \quad [\mathrm{C_2O_4}^{2-}] = 1.52 \times 10^{-5}\ \mathrm{mol \cdot L^{-1}}$$

$$Q = (1.52 \times 10^{-4})(1.52 \times 10^{-5}) = 2.3 \times 10^{-9}$$

$$Q = K_s \Rightarrow \text{Saturation equilibrium}$$

Medical significance: Critical threshold before stone formation

▷ **Option 3: Q $> K_s$ (Supersaturation and Precipitation) - Danger Domain**
Thermodynamic interpretation:

$$\Delta G = RT\ln\left(\frac{Q}{K_s}\right) > 0 \Rightarrow \text{Spontaneous precipitation}$$

Precipitation mechanisms:

a) **Homogeneous nucleation:** Spontaneous formation of critical nuclei
b) **Heterogeneous nucleation:** Germination on existing surfaces
c) **Crystal growth:** Ionic accretion on nuclei

Observed clinical phenomena:

- Metastable supersaturation: $Q > K_s$ without immediate precipitation
- Delayed precipitation: Nucleation or inhibitor effect
- Explosive growth: Once nucleation is initiated

Critical clinical example:

$$\begin{aligned}\text{Pathological urine:} [Ca^{2+}] = 5 \times 10^{-3}\ \text{M},\ [C_2O_4{}^{2-}] = 1 \times 10^{-3}\ \text{mol} \cdot \text{L}^{-1} \\ Q = (5 \times 10^{-3})(1 \times 10^{-3}) = 5 \times 10^{-6} \\ K_s = 2.3 \times 10^{-9} \\ Q/K_s = \frac{5 \times 10^{-6}}{2.3 \times 10^{-9}} \approx 2174 \Rightarrow \text{High risk of lithiasis}^{(41)}\end{aligned}$$

Diagnosis: Q and K_s

a) **Measure ionic concentrations** $[A^{b+}]$ and $[X^{a-}]$
b) **Calculate** $Q = [M^{b+}]^a[X^{a-}]^b$
c) **Compare to known** K_s for the compound
d) **Clinical decision:**
   - **If** $Q < 0.8K_s$: Stability guaranteed, no action
   - **If 0.8** $K_s < Q < K_s$: Enhanced monitoring
   - **If** $Q > K_s$: Immediate therapeutic intervention
   - **If** $Q > 2K_s$: Therapeutic emergency
e) **Corrective actions:**
   - **Dilution**: Reduction of Q by increasing volume
   - **Complexation**: Reduction of free ionic concentrations
   - **pH modification**: Change in ionic species
   - **Elimination**: Reduction of intake or increased excretion

In clinical practice, several factors can influence solubility:

- **Body temperature** (37 °C instead of 25 °C) slightly modifies solubility
- **pH** can transform certain ions and change their solubility
- **Other substances** in the medium can "trap" ions and prevent precipitation
- **Proteins** present in biological fluids can protect against crystal formation

In summary: The Q/K calculation gives an excellent basic prediction, but the human body is a complex system where other factors come into play.

6.4.2.3 Advanced Clinical Applications of Prediction

▷ **Prediction of Kidney Stones: Quantitative Approach Measured biological parameters:**

$$\begin{aligned}[Ca^{2+}]_{\text{urine}} &= 2.5 \times 10^{-3}\ \text{mol} \cdot \text{L}^{-1} \\ [C_2O_4{}^{2-}]_{\text{urine}} &= 5.0 \times 10^{-4}\ \text{mol} \cdot \text{L}^{-1} \\ [PO_4{}^{3-}]_{\text{urine}} &= 2.0 \times 10^{-2}\ \text{mol} \cdot \text{L}^{-1} \\ \text{pH} &= 6.2\end{aligned}$$

Calculations of ionic products:

$$\begin{aligned}Q(CaC_2O_4) &= (2.5 \times 10^{-3})(5.0 \times 10^{-4}) = 1.25 \times 10^{-6} \\ Q(Ca_3(PO_4)_2) &= (2.5 \times 10^{-3})^3(2.0 \times 10^{-2})^2 = 6.25 \times 10^{-10} \\ K_s(CaC_2O_4) &= 2.3 \times 10^{-9} \\ K_s(Ca_3(PO_4)_2) &= 2.1 \times 10^{-33}\end{aligned}$$

Risk analysis:

- CaC_2O_4: $Q/K_s = 1.25 \times 10^{-6}/2.3 \times 10^{-9} \approx 543 \Rightarrow$ High risk
- $Ca_3(PO_4)_2$: $Q/K_s = 6.25 \times 10^{-10}/2.1 \times 10^{-33} \approx 3 \times 10^{23} \Rightarrow$ Very high risk[(49)]

Therapeutic recommendations:[49]

a) Aggressive hydration to dilute to have $Q < K_s$
b) Dietary oxalate restriction
c) Urinary alkalinization for phosphates
d) Close monitoring $Q/K_s < 1$

▷ **Formation of Gallstones: Multiple Mechanisms**

Main components:

- **Cholesterol** (80%): Solubility dependent on bile salts
- **Bile pigments** (20%): Calcium bilirubinate
- **Calcium salts**: Carbonate, phosphate, palmitate

Complete thermodynamic analysis: For bilirubin.

$$\mathrm{Bil_2Ca_{(s)}} \rightleftharpoons 2\,\mathrm{Bil^-_{(aq)}} + \mathrm{Ca^{2+}_{(aq)}}$$

$$K_s \approx 10^{-10}$$

$$\text{Normal bile: } Q = [Bil^-]^2[Ca^{2+}] \approx 10^{-12} < K_s$$

$$\text{Lithogenic bile: } Q \approx 10^{-8} > K_s$$

Concrete Case: The Mystery of Kidney Stones

Clinical case

Patient case: 45-year-old man, renal colic

Urinary data:

- $[\mathrm{Ca^{2+}}] = 2.5 \times 10^{-3}\,\mathrm{mol \cdot L^{-1}}$
- $[\mathrm{C_2O_4^{2-}}] = 5.0 \times 10^{-4}\,\mathrm{mol \cdot L^{-1}}$
- pH = 6.2

Analysis:

$$Q = (2.5 \times 10^{-3})(5.0 \times 10^{-4}) = 1.25 \times 10^{-6}$$

$$K_s = 2.3 \times 10^{-9} \Rightarrow Q/K_s \approx 543$$

Risk: Very high (inevitable precipitation)
Treatment: Hydration + oxalate restriction + potassium citrate

Favoring factors:

a) **Supersaturation** ($Q > K_s$): Hypersecretion of cholesterol
b) **Accelerated nucleation**: Mucin as heterogeneous nucleus
c) **Inhibitor deficiency**: Apolipoproteins A1 and A2
d) **Biliary stasis**: Concentration by water resorption

Preventive approaches:

- **Ursodeoxycholic acid**: Reduction of cholesterol secretion
- **Cholagogue**: Regular bile evacuation
- **Nutritional control**: Reduction of saturated fats
- **Monitoring**: Ultrasound and Q/K_s measurement

6.4.3 Factors Controlling Solubility:

Analogy (1 sentence): In solution, ions "choose" between remaining solvated or organizing into a crystal lattice.

Two major factors modulate the solubility of sparingly soluble salts: **the common ion effect** and **pH** (via acid-base speciation).

6.4.3.1 The Common Ion Effect: When Chemistry Protects Our Health

Principle We speak of a **common ion effect** when an ion already present in the dissolution equation is added to a solution in equilibrium with a solid.[31] The increase in concentration (or activity) of this ion increases the ionic product Q and shifts the equilibrium in the direction that brings it back toward K_s, which decreases the solubility of the solid (Le Chatelier's principle).

Example (classic): silver chloride

$$\mathrm{AgCl(s)} \rightleftharpoons \mathrm{Ag^+(aq) + Cl^-(aq)}$$

If $\mathrm{Cl^-}$ is added (for example via $\mathrm{NaCl(aq)}$), then $Q = [\mathrm{Ag^+}][\mathrm{Cl^-}]$ increases. The system evolves to the left: $\mathrm{AgCl(s)}$ precipitates and the concentration of $\mathrm{Ag^+}$ decreases.

Link with Q and K_s The addition of a common ion generally increases Q; if $Q > K_s$, precipitation is **thermodynamically favored** (but may be delayed by a nucleation barrier, thus by kinetics).
For a better understanding, here is a **quantitative view: case of calcium fluoride**.
Dental enamel undergoes repeated acid attacks; fluoride can limit demineralization via the common ion effect.

Before	$\mathrm{CaF_{2(s)}}$	$\rightleftharpoons$	$\mathrm{Ca^{2+}_{(aq)}}$	+	$\mathrm{2\,F^-_{(aq)}}$
			s_0		$2s_0$
$\mathrm{F^-}$ source	$\mathrm{NaF_{(s)}}$	$\rightleftharpoons$	$\mathrm{Na^+_{(aq)}}$	+	$\mathrm{F^-_{(aq)}}$
common ion			C		C
After	$\mathrm{CaF_{2(s)}}$	$\rightleftharpoons$	$\mathrm{Ca^{2+}_{(aq)}}$	+	$\mathrm{2\,F^-_{(aq)}}$
			s		$2s + C$

Solubility in pure water:

$$K_s = [\mathrm{Ca^{2+}}][\mathrm{F^-}]^2 = s(2s)^2 = 4s^3 \quad \Rightarrow \quad s_0 = \sqrt[3]{\frac{K_s}{4}} = 2.1 \times 10^{-4}\ \mathrm{mol\,L^{-1}}$$

After addition of NaF at concentration $C = 0.01\ \mathrm{mol\,L^{-1}}$:

$$[\mathrm{Ca^{2+}}] = s, \qquad [\mathrm{F^-}] = C + 2s \simeq C \quad (C \gg 2s)$$

$$K_s = [\mathrm{Ca^{2+}}][\mathrm{F^-}]^2 \simeq sC^2 \quad \Rightarrow \quad s \simeq \frac{K_s}{C^2} = 3.9 \times 10^{-7}\ \mathrm{mol\,L^{-1}}$$

$$\frac{s_0}{s} \approx 538$$

Physical significance and clinical implications: The addition of fluoride imposes a high concentration of $\mathrm{F^-}$ in solution, which greatly decreases the solubility of $\mathrm{CaF_2}$ by common ion effect. Under the calculation conditions ($C = 0.01\ \mathrm{mol.L^{-1}}$), solubility is reduced by a factor $\approx 5 \times 10^2$, which favors the formation/maintenance of a superficial fluoride *reservoir* ($\mathrm{CaF_2}$-type deposits) and limits mineral loss during acid episodes. In the longer term, fluoride can also promote less soluble mineralization (fluorapatite), increasing the overall resistance of enamel to acid attacks.

Dental application: protective role of fluoride and quantitative demonstration Dental enamel, a true biological armor, is composed primarily of hydroxyapatite $\mathrm{Ca_{10}(PO_4)_6(OH)_2}$.[(42)] Permanently subjected to acid attacks from diet and bacteria, it tends to demineralize. **Fluoride** ($\mathrm{F^-}$) then acts as a chemical shield, via two complementary ideas: (i) dissolution/precipitation equilibria (common ion effect, $\mathrm{CaF_2}$-type deposits) and (ii) $\mathrm{OH^-/F^-}$ substitution potentially leading to less soluble apatite.

a) **Ionic substitution:** Fluoride ions partially replace hydroxide ions ($\mathrm{OH^-}$) in the hydroxyapatite crystal lattice.
b) **Fluorapatite formation:**

$$\mathrm{Ca_{10}(PO_4)_6(OH)_2 + 2\,F^- \rightleftharpoons Ca_{10}(PO_4)_6F_2 + 2\,OH^-}$$

c) **Result:** an overall more stable mineral phase less sensitive to acid attacks.

Comparative solubility data (order of magnitude):[(42)]

Hydroxyapatite (HA)	:	$K_s \sim 10^{-117}$
Fluorapatite (FA)	:	$K_s \sim 10^{-121}$
Ratio	:	$\sim 10^4$ (FA thermodynamically more stable)

Demonstration (simplified framework) Dissolution equilibrium of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$:

$$Ca_{10}(PO_4)_6(OH)_{2(s)} \rightleftharpoons 10\,Ca^{2+} + 6\,{PO_4}^{3-} + 2\,OH^-$$

$$K_s(\mathrm{HA}) = [Ca^{2+}]^{10}[{PO_4}^{3-}]^6[OH^-]^2 \quad \text{(written in concentrations; rigorously in activities).}$$

OH^-/F^- Substitution Fluoride competes with hydroxide ions according to:

$$Ca_{10}(PO_4)_6(OH)_2 + 2\,F^- \rightleftharpoons Ca_{10}(PO_4)_6F_2 + 2\,OH^-$$

Under simplifying assumptions (same effective activities of Ca^{2+} and ${PO_4}^{3-}$ in both equilibria), one can relate the order of magnitude of the exchange equilibrium constant to the ratio of solubility products:

$$K_{\mathrm{eq}} \sim \frac{[OH^-]^2}{[F^-]^2} \sim \frac{K_s(\mathrm{HA})}{K_s(\mathrm{FA})} \sim 10^4.$$

Influence of pH on solubility **Objective (simplified model).** In acidic medium (pH = 4.5), the effect of pH is illustrated via the OH^- ion and a qualitative comparison between hydroxyapatite (HA) and fluorapatite (FA) is made. *Note:* the real "enamel–saliva" system is more complex (activities, phosphate speciation, complexation), so the calculation below mainly gives an **order of magnitude**.
At pH = 4.5:

$$[OH^-] = 10^{-(14-4.5)} = 10^{-9.5}$$

For hydroxyapatite:

$$[Ca^{2+}]_{\mathrm{HA}} \approx \left(\frac{K_s(\mathrm{HA})}{[OH^-]^2\,[{PO_4}^{3-}]^6}\right)^{1/10}$$

For fluorapatite:

$$[Ca^{2+}]_{\mathrm{FA}} \approx \left(\frac{K_s(\mathrm{FA})}{[F^-]^2\,[{PO_4}^{3-}]^6}\right)^{1/10}$$

Assuming, for comparison, that $[{PO_4}^{3-}]$ is constant and taking an indicative salivary fluoride value $[F^-] = 10^{-4}\ \mathrm{mol.L^{-1}}$, we obtain:

$$\frac{[Ca^{2+}]_{\mathrm{HA}}}{[Ca^{2+}]_{\mathrm{FA}}} \approx \left(\frac{K_s(\mathrm{HA})}{K_s(\mathrm{FA})} \times \frac{[F^-]^2}{[OH^-]^2}\right)^{1/10}$$

$$\approx \left(10^4 \times \frac{(10^{-4})^2}{(10^{-9.5})^2}\right)^{1/10} = (10^4 \times 10^{11})^{1/10} = 10^{1.5} \approx 32$$

Interpretation (cautious) In this simplified framework, the presence of fluoride and the lower intrinsic solubility of FA lead to a lower release of Ca^{2+} than with HA in acidic medium (order of magnitude $\sim 10^1$).

Usual fluoride concentrations (references)

- Fluoridated drinking water (target value): $\approx 0.7\,\mathrm{mg.L^{-1}}$.
- "Standard" toothpastes: typically $\approx$ 1000–1500 ppm fluoride.
- Professional fluoride varnish: 22,600 ppm (5% NaF, $\approx$ 2.26% fluoride).

Conclusion (corrected formulation). Fluorapatite is thermodynamically more stable than hydroxyapatite (via lower K_s) and, in acidic medium, fluoride-enriched enamel is overall more resistant to demineralization; the exact quantitative factors depend on pH, phosphate speciation, and activities in saliva.

Dental application[50]

Clinical case

Patient case: 8-year-old child, multiple caries
Examination: DMS = 4.0 (high), low salivary fluoride
Strategy: Application of fluoride varnish (22,600 ppm)
Mechanism: Local increase of F^- (fluoride reservoir, remineralization) and possible formation of less soluble apatite
Result: DMS reduced to 1.5 after 6 months
Follow-up: Quarterly monitoring of oral pH

6.4.3.2 pH control: acid–base and solubility

Principle: pH influences the solubility of many ionic solids as soon as one of their ions belongs to an acid–base couple. According to Le Chatelier's principle, the consumption of an ion produced by dissolution (by protonation or deprotonation) shifts the dissolution equilibrium in the direction that **favors dissolution**; conversely, increasing the deprotonated form can **favor precipitation**.[51]

Example: calcium deposits and urinary pH Calcium carbonate ($CaCO_3$) is sparingly soluble; its behavior depends strongly on carbonate equilibria.[46]

$$CaCO_{3(s)} \rightleftharpoons Ca^{2+}_{(aq)} + {CO_3}^{2-}{}_{(aq)} \qquad K_s = [Ca^{2+}][{CO_3}^{2-}]$$

The carbonate ion is basic and is protonated to bicarbonate:

$${CO_3}^{2-}{}_{(aq)} + H_3O^+_{(aq)} \rightleftharpoons {HCO_3}^-{}_{(aq)} + H_2O$$

Pathophysiological link (general idea). When a urinary tract infection by urease-producing bacteria alkalinizes urine, the precipitation of certain salts (notably phosphate/ammonium–magnesium and carbonated apatites) is favored.

(Pedagogical note) The clinical example "infection ⇒ alkaline urine ⇒ stones" is robust, but the major species is not necessarily pure $CaCO_3$; rather, struvite and carbonate-apatite matrices are observed.

Quantitative view (simplified model): effect of pH on apparent solubility **Assumptions:** ideal solution (activities ≈ concentrations), only protonation ${CO_3}^{2-} \longrightarrow {HCO_3}^-$ is considered, and $CO_{2/}H_2CO_3$ is neglected.
At 25°C, we take an order of magnitude $K_s \approx 3.3 \times 10^{-9}$.
Reference solubility in pure water (without acid–base). If $[Ca^{2+}] = [{CO_3}^{2-}] = s_0$, then:

$$s_0 = \sqrt{K_s} = \sqrt{3.3 \times 10^{-9}} \approx \boxed{5.7 \times 10^{-5}\ \text{mol}\,.\text{L}^{-1}}$$

Acid–base coupling (imposed pH)

Demonstration 1: With the acidity constant K_a
1. The equilibria involved: Acid-base (deprotonation direction):

$${HCO_3}^- \rightleftharpoons {CO_3}^{2-} + H^+ \quad ; \quad K_a = \frac{[{CO_3}^{2-}][H^+]}{[{HCO_3}^-]} = 10^{-pK_{a2}} = 10^{-10.33}$$

2. Mass balance:
The solubility s represents all dissolved calcium, so $[Ca^{2+}] = s$.
All carbonate from the solid is distributed between ${CO_3}^{2-}$ and ${HCO_3}^-$:

$$s = [{CO_3}^{2-}] + [{HCO_3}^-]$$

3. Expression of $[{HCO_3}^-]$ as a function of $[{CO_3}^{2-}]$:

From the K_a expression we obtain:

$$[HCO_3^-] = \frac{[CO_3^{2-}][H^+]}{K_a}$$

4. **Substitution into the mass balance:**

$$s = [CO_3^{2-}] + \frac{[CO_3^{2-}][H^+]}{K_a} = [CO_3^{2-}]\left(1 + \frac{[H^+]}{K_a}\right)$$

Hence:

$$[CO_3^{2-}] = \frac{s}{1 + \frac{[H^+]}{K_a}}$$

5. **Use of the solubility product:**
$K_s = [Ca^{2+}][CO_3^{2-}] = s \times [CO_3^{2-}]$
Substituting $[CO_3^{2-}]$:

$$K_s = s \times \frac{s}{1 + \frac{[H^+]}{K_a}} = \frac{s^2}{1 + \frac{[H^+]}{K_a}}$$

6. **Final expression of solubility:**

$$s^2 = K_s\left(1 + \frac{[H^+]}{K_a}\right)$$

$$\boxed{s = \sqrt{K_s\left(1 + \frac{[H^+]}{K_a}\right)} = \sqrt{K_s\left(1 + \frac{10^{-pH}}{10^{-10.33}}\right)} = \sqrt{K_s\left(1 + 10^{10.33-pH}\right)}}$$

Demonstration 2: With the protonation constant K

1. **The equilibria involved:**
Dissolution (identical):

$$CaCO_3(s) \rightleftharpoons Ca^{2+} + CO_3^{2-} \quad ; \quad K_s = [Ca^{2+}][CO_3^{2-}]$$

Acid-base (protonation direction):

$$CO_3^{2-} + H_3O^+ \rightleftharpoons HCO_3^- + H_2O \quad ; \quad K_a = \frac{[HCO_3^-]}{[CO_3^{2-}][H_3O^+]} = 10^{pK_{a2}} = 10^{10.33}$$

2. **Mass balance:**
we have: $[Ca^{2+}] = s$ and $s = [CO_3^{2-}] + [HCO_3^-]$

3. **Expression of $[HCO_3^-]$ as a function of $[CO_3^{2-}]$:**
From the K_a expression we directly obtain:

$$[HCO_3^-] = K[CO_3^{2-}][H_3O^+]$$

4. **Substitution into the mass balance:**

$$s = [CO_3^{2-}] + K[CO_3^{2-}][H_3O^+] = [CO_3^{2-}]\left(1 + K[H_3O^+]\right)$$

Hence:

$$[CO_3^{2-}] = \frac{s}{1 + K[H_3O^+]}$$

5. **Use of the solubility product:**
$K_s = [Ca^{2+}][CO_3^{2-}] = s \times [CO_3^{2-}]$
Substituting $[CO_3^{2-}]$:

$$K_s = s \times \frac{s}{1 + K[H_3O^+]} = \frac{s^2}{1 + K[H_3O^+]}$$

6. **Final expression of solubility:**

$$s^2 = K_s\,(1 + K[\mathrm{H_3O^+}])$$

$$\boxed{s = \sqrt{K_s\,(1 + K[\mathrm{H_3O^+}])} = \sqrt{K_s\,(1 + K \times 10^{-pH})} = \sqrt{K_s\,(1 + 10^{10.33-pH})}}$$

Note: The two expressions are equivalent because $K = \dfrac{1}{K_a} = 10^{pK_{a2}}$ and $[\mathrm{H_3O^+}] = [\mathrm{H^+}] = 10^{-pH}$.

Caution

The Difference between acidity constant K_a and protonation constant K

It is essential to understand that the constants K_a and K describe the **same chemical equilibrium** but in **opposite directions**. They are simply inverses of each other:

$$\boxed{K = \frac{1}{K_a} = 10^{pK_a}}$$

For the $\mathrm{HCO_3^-}$ / $\mathrm{CO_3^{2-}}$ couple: With K_a (acidity constant)

$$\mathrm{HCO_3^-} \rightleftharpoons \mathrm{CO_3^{2-}} + \mathrm{H^+}$$
$$K_a = \frac{[\mathrm{CO_3^{2-}}][\mathrm{H^+}]}{[\mathrm{HCO_3^-}]} = 10^{-pK_{a2}} = 10^{-10.33}$$

K_a characterizes the strength of the acid $\mathrm{HCO_3^-}$ to donate a proton.
With K (protonation constant)

$$\mathrm{CO_3^{2-}} + \mathrm{H^+} \rightleftharpoons \mathrm{HCO_3^-}$$
$$K = \frac{[\mathrm{HCO_3^-}]}{[\mathrm{CO_3^{2-}}][\mathrm{H^+}]} = 10^{pK_{a2}} = 10^{10.33}$$

K characterizes the strength of the base $\mathrm{CO_3^{2-}}$ to capture a proton.

Mathematical relationship The two constants are rigorously inverses:

$$K = \frac{1}{K_a} \quad \text{and} \quad K_a = \frac{1}{K}$$

$$K = 10^{pK_a} = 10^{10.33} \approx 2.1 \times 10^{10}$$
$$K_a = 10^{-pK_a} = 10^{-10.33} \approx 4.7 \times 10^{-11}$$

What to remember

- A constant can be very small ($K_a = 10^{-10.33} \ll 1$) or very large ($K = 10^{10.33} \gg 1$) depending on the direction in which the reaction is written, but they describe exactly the same chemical reality.
- In $\mathrm{CaCO_3}$ solubility calculations, both formulations are perfectly equivalent:

$$s = \sqrt{K_s\left(1 + \frac{[\mathrm{H^+}]}{K_a}\right)} = \sqrt{K_s\,(1 + K[\mathrm{H^+}])} = \sqrt{K_s\,(1 + K \cdot 10^{-pH})}$$

- The choice of one or the other is a matter of convenience:
  - K_a is the universal convention in acidity (data tables)
  - K is sometimes more practical when working from the protonation perspective of a base, as in the study of dissolution in acidic medium

Memory aid

If pK_a is large (strong conjugate base), then $K = 10^{pK_a}$ is large: the base captures protons very easily.
This is exactly what happens here with CO_3^{2-} ($pK_a = 10.33 \Rightarrow K \approx 2 \times 10^{10}$), which explains why the solubility of $CaCO_3$ increases so much in acidic medium: CO_3^{2-} ions are immediately protonated to HCO_3^-, shifting the dissolution equilibrium to the right.

In summary: Do not be confused by these two notations! Whether you use K_a or K, you are doing the same calculations and obtaining the same results. It is like looking at a hill from two opposite sides: the slope does not have the same steepness depending on the direction you climb it, but it is the same hill!

Case N°1: normal urine (pH = 6.0)[44]

$$[H_3O^+] = 10^{-6.0} = 1.0 \times 10^{-6} \text{ mol} \cdot \text{L}^{-1}$$

$$s_6 = \sqrt{K_s\,(1 + K\,10^{-6})} \approx \sqrt{(3.3 \times 10^{-9})\,(1 + 2.0 \times 10^{4})} \approx \boxed{8.1 \times 10^{-3} \text{ mol} \cdot \text{L}^{-1}}$$

$$\frac{s_6}{s_0} \approx \frac{8.1 \times 10^{-3}}{5.7 \times 10^{-5}} \approx 142$$

Significance: At pH = 6, the protonation of CO_3^{2-} to HCO_3^- strongly consumes CO_3^{2-}, which decreases $[CO_3^{2-}]_{\text{free}}$ and favors the dissolution of the solid (equilibrium shift).

Case N°2: physiological pH (pH = 7.0)[52]

$$[H_3O^+] = 10^{-7.0} = 1.0 \times 10^{-7} \text{ mol} \cdot \text{L}^{-1}$$

$$s_7 = \sqrt{K_s\,(1 + K\,10^{-7})} = \sqrt{(3.3 \times 10^{-9})\,(1 + 2000)} \approx \boxed{2.57 \times 10^{-3} \text{ mol} \cdot \text{L}^{-1}}$$

$$\frac{s_7}{s_0} \approx 45.1$$

Significance: At pH = 7, the solubility remains largely above s_0, but lower than at pH = 6, because $[H_3O^+]$ is ten times weaker.

Case N°3: alkaline urine (pH = 8.0)

$$[H_3O^+] = 10^{-8.0} = 1.0 \times 10^{-8} \text{ mol} \cdot \text{L}^{-1}$$

$$s_8 = \sqrt{K_s\,(1 + K\,10^{-8})} = \sqrt{(3.3 \times 10^{-9})\,(1 + 200)} \approx \boxed{8.14 \times 10^{-4} \text{ mol} \cdot \text{L}^{-1}}$$

$$\frac{s_8}{s_0} \approx 14.3$$

Significance: At pH = 8, the protonation effect is much weaker: less H_3O^+ is available, so the consumption of CO_3^{2-} decreases and solubility drops.

Comparative summary:

pH	Solubility ($\text{mol} \cdot \text{L}^{-1}$)	Ratio s/s_0	Trend
Theoretical (pure water)	5.7×10^{-5}	1	Reference
pH = 6	8.1×10^{-3}	142	Strong increase
pH = 7	2.57×10^{-3}	45.1	Marked increase
pH = 8	8.14×10^{-4}	14.3	Moderate increase

Conclusion: In this model (CO_3^{2-}/HCO_3^- couple only), solubility **decreases as pH increases** over the 6–8 range; it is therefore **maximal at pH = 6** (the most acidic studied). This dependence comes from the term $K10^{-pH}$: the more acidic the medium, the more effective the protonation of CO_3^{2-}, and the more the dissolution of $CaCO_3$ is favored.

Clinical significance and therapeutic implications

1. Prevention of kidney stones

- **pH and stone type**: high urinary pH favors **calcium phosphate** stones (e.g., carbonate apatite, brushite), particularly beyond ~ 6.8 for certain crystals.[49]
- **Practical objective**: avoid prolonged alkalinization in Ca-phosphate stone formers; the exact pH target should be discussed according to etiology and metabolic workup.
- **Non-pharmacological measures**: adequate hydration and monitoring of urinary parameters (pH, urine volume, calciuria, citraturia) in at-risk patients.

2. Management of urinary tract infections (infection stones)

- **Diagnostic orientation**: urinary pH $\gtrsim 7$ is suspicious for infection/infection stones and should prompt investigation for urease-producing organisms (especially *Proteus*; other organisms may be involved).
- **Central clinical message**: manage the infection (appropriate antibiotic therapy) and, in the case of struvite stones, appropriate urological treatment; pH is a *marker* and a *secondary lever*.
- **Prevention**: avoid persistent alkalinization in infection stone patients, as it promotes the precipitation of sparingly soluble salts.

3. Management of acid-base disorders

- **Chronic metabolic acidosis**: may be associated with altered bone metabolism and increased stone risk depending on the context (notably certain tubular acidoses).
- **Excessive alkalinization**: may increase the risk of calcium phosphate precipitation in predisposed patients.
- **Renal compensation**: the kidney modulates acid excretion and urinary composition, directly linking acid-base balance and crystallization risk.

4. Concrete therapeutic implications

- **Alkalinization (uric acid stones)**: treatment with alkalinizing agents (e.g., potassium citrate) typically aims for a urinary pH around 6.0–6.5 (prevention) and rather 6.5–7.0 in certain dissolution strategies, avoiding too high a pH.
- **Ca-phosphate**: caution with prolonged alkalinization; high pH is a recognized risk factor.
- **Hydration**: a universal measure, as it decreases supersaturation by lowering urinary ionic concentrations.
- **Monitoring**: pH test strips and specialized follow-up according to profile (metabolic workup, imaging if indicated).

5. Preventive strategies

- **At-risk patients**: history of lithiasis, recurrences, suspected renal tubular acidosis, recurrent urinary tract infections, etc.
- **Education**: self-monitoring of pH (especially useful during alkalinization/acidification treatments) with individualized targets.
- **Follow-up**: adapt strategy to stone analysis and metabolic workup.

Summary table of strategies

Type of urinary stone	Recommended pH	Main strategy	Treatment examples
Calcium phosphate stones	Avoid too high pH	Do not alkalinize too long	Lower pH if necessary (specific cases)
Uric acid stones	Increase pH	Alkalinize in a controlled manner	Potassium citrate (sometimes with bicarbonate)
Infection stones (struvite)	Often > 7	Treat infection + urological management	Adapted antibiotics, stone removal
Suspected renal tubular acidosis	Inappropriate pH (often high)	Diagnose cause + correct	Controlled alkalinization (specialist advice)

Clinical conclusion Understanding pH–speciation–supersaturation relationships allows linking a simple chemical model to practical decisions. The goal is not to reach a single "ideal pH," but to individualize the pH target according to stone type, metabolic workup, and infectious context.

General conclusion pH–solubility modeling illustrates the role of pH on carbonate system speciation and on the dissolution/precipitation of calcium salts.

Synthesis of mechanisms

- pH controls HCO_3^-/CO_3^{2-} speciation (via pK_a2) and indirectly influences $CaCO_3$ dissolution.
- In the simplified model used here, solubility **increases as pH decreases** over 6–8 (maximum at the most acidic pH studied).
- The theory/experiment gap reminds us that biological media are non-ideal (activities, complexation, kinetics, etc.).

Clinical scope

- Lithiasis prevention relies on adapting urinary pH to the **stone type** (uric acid, Ca-phosphate, and infection).
- Therapeutic strategies modify urinary supersaturation (pH, urine volume, citrate, etc.) rather than "solubility" alone.

Integrative perspective "From the chemical equation to the therapeutic decision, understanding urinary pH links ionic speciation, supersaturation, and crystallization risk."

Caution

The observation

- **Theoretical (ideal) calculation**: $s_0^{th} = 5.7 \times 10^{-5}$ mol $\cdot$ L^{-1} (from $\sqrt{K_s}$)
- **Experimental (real) measurement**: $s_0^{exp} = 2.4 \times 10^{-6}$ mol $\cdot$ L^{-1}
- **Ratio**: $\frac{s_0^{th}}{s_0^{exp}} \approx 24$ (theory overestimates by a factor of 24)

Explanations for the divergence

1. Real experimental conditions (non-ideality)

- **Activities**: in concentrated ionic media, the activity coefficient $\gamma \neq 1$. Caution: the approximation $[i] = a_i$ (concentration = activity) is no longer valid.
- **Kinetics**: dissolution/precipitation can be slow; equilibrium may not be reached during measurement.
- **Speciation**: part of the species may not be in **free** form (formation of ion pairs $CaHCO_3^+$, $CaCO_3$...); yet K_s only applies to free species.

Definition

Speciation is the study of the **distribution** of a chemical element among the different **chemical forms** (species) it can adopt in a given medium.

Why is this important?

- Because properties (toxicity, bioavailability, reactivity) depend on the chemical form, not just the total amount.
- Because equilibrium constants (K_s, K_a, etc.) only apply to **free** species, not complexed or associated species.

Pedagogical analogy:

A classroom	**A chemical solution**
30 people (total)	$C_T = 0.1$ mol/L (total)
15 students, 10 parents, 5 teachers	CO_3^{2-}, HCO_3^-, H_2CO_3, $CaHCO_3^+$
Only students can go out for recess	Only free ions participate in K_s

Application to your problem: When experimental solubility of $CaCO_3$ is measured, one obtains $s_{exp} = [Ca]_{total}$. But in K_s, only $[Ca^{2+}]_{free}$ matters. The difference between these two values is **speciation**.

In summary:

$$\underbrace{[Ca]_{total}}_{\text{what is measured}} = \underbrace{[Ca^{2+}]_{free}}_{\text{only one involved in } K_s} + \underbrace{[CaHCO_3^+] + [CaCO_3^0] + \cdots}_{\text{complexed forms (speciation)}}$$

Speciation explains why **measured** solubility differs from **ideal** solubility (calculated from K_s).

2. Crystalline polymorphism

- **Calcite / aragonite / vaterite**: these three polymorphs of $CaCO_3$ have different solubilities; a real sample may be a mixture or evolve (aging, recrystallization). Calcite (the most stable form) has the lowest K_s.

3. Biological and chemical effects

- **Inhibitors/ligands** (citrate, Mg^{2+}, pyrophosphate, etc.): can modify nucleation, crystal growth, and apparent solubility.
- **Organic matter**: protein adsorption, surface interactions, heterogeneity of the biological medium (urine, natural waters...).

Interpretation: "The theoretical model is not wrong: it is idealized."

- The calculation assumes: pure water, activities ≈ concentrations, equilibrium reached, no interfering interactions.
- The measurement reflects: complex medium, speciation, non-ideality, kinetics, and biological effects.
- The essential point to retain is the **trend** (the more acidic the medium, the more $CaCO_3$ dissolves), even if the absolute values differ.

Final conclusion The value 2.4×10^{-6} mol · L^{-1} corresponds to an **apparent solubility** under real conditions, while 5.7×10^{-5} mol · L^{-1} corresponds to an **ideal solubility** derived from K_s alone. Both approaches are complementary: one for practice (medicine, geochemistry), the other for fundamental understanding of equilibria.

Important

Solution chemistry is not just an abstraction: it governs crystallization and lithiasis prevention.

Example N°2 "Bone equilibrium": Calcium carbonate ($CaCO_3$) plays an essential role in **bone mineralization** and in **blood pH regulation**. In biological tissues, it coexists with hydroxyapatite and participates in calcium ionic equilibrium.

$$CaCO_{3(s)} \rightleftharpoons Ca^{2+}_{(aq)} + {CO_3}^{2-}{}_{(aq)}$$

This equilibrium is controlled by blood pH (≈ 7.4) and blood buffer systems (${H_2CO_3}_/{HCO_3}^-$). When the medium becomes acidic (acidosis), protons react with the carbonate ion:

$${CO_3}^{2-}{}_{(aq)} + {H_{(aq)}}^+ \rightleftharpoons {HCO_3}^-{}_{(aq)}$$

Thus, a decrease in blood pH leads to **partial dissolution of bone calcium carbonate**, releasing Ca^{2+} to buffer H^+ ions. This mechanism contributes to maintaining acid-base balance but weakens bone structure in the long term.

Quantitative View: Influence of pH on $CaCO_3$ Solubility

$$CaCO_{3(s)} \rightleftharpoons Ca^{2+}_{(aq)} + {CO_3}^{2-}{}_{(aq)} \quad \text{with:} \quad K_s = 3.3 \times 10^{-9}$$

In normal plasma (pH = 7.4), we have:

$$[H^+] = 10^{-7.4} = 4.0 \times 10^{-8}\,\text{mol/L}$$

The acidification reaction:

$${CO_3}^{2-} + H^+ \rightleftharpoons {HCO_3}^- \quad \text{with:} \quad K = 10^{10.3}$$

Bone equilibrium	$CaCO_{3(s)}$	$\rightleftharpoons$	Ca^{2+}	+	${CO_3}^{2-}$
			s		s
In acidosis	${CO_3}^{2-}$	+	H^+	$\rightleftharpoons$	${HCO_3}^-$
			$[H^+]$		
New equilibrium	$CaCO_{3(s)}$	$\rightleftharpoons$	Ca^{2+}	+	${CO_3}^{2-}$
			s'		s' - x

The two fundamental equations are:

$$K_s = [Ca^{2+}][{CO_3}^{2-}] = s'(s' - x)$$

$$K = \frac{[{HCO_3}^-]}{[{CO_3}^{2-}][H^+]} = \frac{x}{(s' - x)[H^+]}$$

Combining and solving, we obtain:

$$\boxed{s' \approx 9.8 \times 10^{-5}\,\text{mol/L}} \quad \text{and} \quad \frac{s'}{s_0} \approx 1.7$$

Biological and clinical significance:
Mild acidosis (pH $\approx$ 7.2) increases calcium carbonate solubility by about 70%, leading to increased release of Ca^{2+} ions into the plasma.[52] This phenomenon allows **temporary compensation of blood pH**, but at the expense of bone mineral density. In patients with chronic acidosis (e.g., renal failure, respiratory disorders), this contributes to **bone demineralization** and bone fragility.
Thus, calcium carbonate acts as a **physiological buffer**, but its excessive dissolution becomes an indicator of metabolic imbalance.

Example N°3: Drug Absorption in the Body pH plays a crucial role in the solubility and absorption of drugs in our body. The stomach (pH $\approx$ 1.5-3.5) and intestine (pH $\approx$ 6-7.5) present very different environments that affect the dissolution of active ingredients.
Case of aspirin (acetylsalicylic acid): Aspirin ($C_9H_8O_4$) is a weak acid (pKa = 3.5) whose solubility varies considerably with pH:[35]

$$C_9H_8O_{4(s)} \rightleftharpoons {C_9H_7O_4^-}_{(aq)} + H^+_{(aq)}$$

Mathematical Demonstration of pH Influence Consider a weak acid HA in equilibrium in water according to the reaction:

$$\mathrm{HA} \rightleftharpoons \mathrm{H^+} + \mathrm{A^-}$$

Step 1: pH We start with the acidity constant:

$$K_a = \frac{[\mathrm{H^+}][\mathrm{A^-}]}{[\mathrm{HA}]} \Rightarrow [\mathrm{H^+}] = K_a \cdot \frac{[\mathrm{HA}]}{[\mathrm{A^-}]} \Rightarrow \boxed{\mathrm{pH} = \mathrm{p}K_a + \log\left(\frac{[\mathrm{A^-}]}{[\mathrm{HA}]}\right)}$$

Step 2: Application to Aspirin Acetylsalicylic acid (aspirin) has: $\mathrm{p}K_a = 3.5$. The ionized fraction (dissociation coefficient) of the drug is given by:

$$\alpha = \frac{[\mathrm{A^-}]}{[\mathrm{A^-}] + [\mathrm{HA}]} = \frac{1}{1 + \frac{[\mathrm{HA}]}{[\mathrm{A^-}]}} = \frac{1}{1 + \frac{[\mathrm{H_3O^+}]}{K_a}}$$

With $[\mathrm{H_3O^+}] = 10^{-\mathrm{pH}}$ and $K_a = 10^{-\mathrm{p}K_a}$:

$$\alpha = \frac{1}{1 + \frac{10^{-\mathrm{pH}}}{10^{-\mathrm{p}K_a}}} = \frac{1}{1 + 10^{\mathrm{p}K_a - \mathrm{pH}}}$$

In the stomach (pH=2):

$$\alpha = \frac{1}{1 + 10^{3.5-2}} = \frac{1}{1 + 10^{1.5}} = \frac{1}{1 + 31.6} = \boxed{0.031}$$

i.e., 3% ionized aspirin, therefore mostly liposoluble (soluble in fats).
In the intestine (pH=7):

$$\alpha = \frac{1}{1 + 10^{3.5-7}} = \frac{1}{1 + 10^{-3.5}} = \frac{1}{1 + 0.000316} \approx \boxed{0.9997}$$

Nearly 100% ionized: high solubility, but low membrane permeability.

Step 3: Interpretation

- When **pH < pKa**, the drug is in non-ionized form (HA), lipophilic, well absorbed in the stomach.
- When **pH > pKa**, it becomes ionized ($\mathrm{A^-}$), hydrophilic, better dissolved in the intestine.

Conclusion This calculation quantitatively shows how pH modulates the distribution of chemical species of a drug, and explains galenic strategies such as enteric-coated forms: mathematically, it is the logarithmic ratio from the law of mass action that translates absorption physiology.
Pharmacological implications:[(35)]

- Acidic drugs are better absorbed in the stomach (non-ionized form more liposoluble)
- Basic drugs are better absorbed in the intestine
- Pharmaceutical formulations take these variations into account to optimize absorption

Quantitative example: Influence of pH on bioavailability
For a drug with a dose of 500 mg and a baseline solubility of 1 mg/mL at neutral pH:

pH	Ionized form (%)	Solubility (mg/mL)	Dissolution time (min)
2.0	5	1.05	476
4.5	50	2.00	250
6.0	90	10.00	50
7.4	99	100.00	5

This spectacular variation explains why some drugs are coated (enteric-coated) to resist gastric acidity and release in the intestine where their solubility is optimal.

Caution

Sometimes another method is found:
In the stomach (pH = 2):

$$\text{Ratio } \frac{[C_9H_7O_4^-]}{[C_9H_8O_4]} = 10^{\text{pH-pKa}} = 10^{2-3.5} = 10^{-1.5} = 0.032 \Leftrightarrow 3\%\text{ionized}$$

$$\alpha = \frac{1}{1+10^{pK_a-\text{pH}}} = \frac{1}{1+10^{3.5-2}} = 0.031 \Leftrightarrow 3\%\text{ionized}$$

The question is:

$$10^{\text{pH-pKa}} \stackrel{?}{=} \frac{1}{1+10^{pK_a-\text{pH}}}$$

The answer is **NO**. To better understand, take the case of (pH = 7):

$$\alpha = \frac{1}{1+10^{3.5-7}} = 0.9997 \Leftrightarrow 99.9\%\text{ionized}$$

$$\text{Ratio } \frac{[C_9H_7O_4^-]}{[C_9H_8O_4]} = 10^{7-3.5} = 10^{3.5} = 3162$$

This means that for 1 molecule of aspirin in non-ionized form ($C_9H_8O_4$), there are 3162 molecules in ionized form ($C_9H_7O_4^-$).

$$\alpha = \frac{[C_9H_7O_4^-]}{[C_9H_7O_4^-]+[C_9H_8O_4]} = \frac{3162}{3162+1} = \frac{3162}{3163} \approx 0.9997 \Leftrightarrow 99.9\%\text{ionized}$$

Therefore, be careful:

$$10^{\text{pH-pKa}} \neq \frac{1}{1+10^{pK_a-\text{pH}}}$$

Common pitfalls and how to avoid them

The 5 most common pitfalls in solubility:

a) **Confusing solubility s and K_s**
- K_s is a **thermodynamic constant** (changes only with temperature)
- s (molar solubility) depends on conditions (pH, common ions, temperature)
- **Example:** For AgCl, K_s is constant but s decreases if NaCl is added

b) **Forgetting stoichiometric coefficients**
- For CaF_2: $[F^-] = 2s$, not s
- For Ag_2CrO_4: $[Ag^+] = 2s$
- **Check:** Electroneutrality must be respected

c) **Neglecting the common ion effect in calculations**
- Always check if an ion present comes from another source
- **Example:** Calculate the solubility of AgCl in 0.1 M NaCl
- $K_s = [Ag^+](0.1 + [Cl^-]) \approx [Ag^+] \times 0.1$

d) **Forgetting the influence of pH**
- Even for non-acid-base salts, pH can affect speciation
- **Example:** $Mg(OH)_2$ is much more soluble in acidic medium
- Always check the pKa of ions in solution

e) **Directly comparing K_s values of different stoichiometries**
- $K_s(AgCl) = 1.8 \times 10^{-10}$ and $K_s(Ag_2CrO_4) = 1.1 \times 10^{-12}$
- One cannot say that Ag_2CrO_4 is "less soluble" without calculating s
- **Solution:** Always calculate s to compare

6.5 Conclusion:

Solubility is a quantifiable heterogeneous equilibrium between a solid phase and dissolved species, characterized by the solubility product K_s. The Q/K_s comparison provides the central criterion for predicting dissolution, saturation, or precipitation, and links chemical calculations to biomedical situations (lithiasis, demineralization, formulation).[31]

On a practical level, two levers dominate the control of the solubility of sparingly soluble salts: the common ion effect and the influence of pH via acid-base speciation.[30] Finally, the discrepancies observed in real media (activities, speciation, kinetics, polymorphism, biological interactions) do not contradict the model: they specify its domain of validity and guide its use.

Transition

The **Solubility** chapter established the link between electronic structure and chemical properties (stability, valence, tendency to lose/gain electrons). This reading becomes essential when the chemical transformation involves an **electron transfer**: this is then called a redox reaction. The chapter **Redox Equilibria** introduces oxidation numbers, oxidant/reductant identification, and balancing methods in acidic or basic media.

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