



What is Steady-State Concentration in Pharmacokinetics?

Need a refresher on what steady-state concentration is, how long it takes to reach steady state, and why this value is key in drug development? Here, we answer the most common questions on steady-state concentration.

What is steady-state concentration?

Steady-state concentration (C_{ss}) occurs when the amount of a drug being absorbed is the same amount that's being cleared from the body when the drug is given continuously or repeatedly.

Here's a good way to think about it: Imagine a coworker is absent, and she left a delicious box of chocolates in her office. You can't resist, and you take two candies. The next morning, you replace the candies so your office mate will never be the wiser. But you later discover she's out again, so you boldly take three chocolates, and replace those the following morning.

As this continues, the chocolates are in a steady state, meaning the number of candies doesn't change day to day. Every time a chocolate is taken, it's replaced in the box. The input rate is the same as the elimination rate.

In pharmacokinetics, those chocolates are drug molecules, and they're being replaced at the same rate—through new doses—that they're being removed from the

body. Steady-state concentration is the time during which the concentration of the drug in the body stays consistent.

For most drugs, the time to reach steady state is [four to five half-lives](#) if the drug is given at regular intervals—no matter the number of doses, the dose size, or the dosing interval. A half-life is how long it takes for half of the drug to be eliminated from the body.

WHY IS THIS?

For simplicity, let's assume we administer a dose every half-life. If a single dose is given every half-life, half of the first dose will be cleared from the body before the next dose.

So, after the second dose, there will be 1.5 doses in the body. Half of that is eliminated and then the next dose is given, meaning there are now 1.75 doses in the body. At dose #5 (after five half-lives), there will be close to two doses in the body, which means one entire dose is eliminated each dosing interval. If we continue dosing at the same frequency, the amount we dose will be eliminated during each dosing interval. As a result, drug concentrations in the body remain constant (steady).

Contact us today:
888.615.5111 | discover@nuventra.com



ANOTHER WAY TO THINK ABOUT STEADY STATE:

- **After Dose 1:** There are 0.5 doses left at the end of the dosing interval. This means we're at 50% steady state.
- **After Dose 2:** There are 1.5 doses in the body, then half is eliminated to leave 0.75 doses (75% steady state).
- **After Dose 3:** There are 1.75 doses in the body, then half is eliminated to leave 0.875 doses (88% steady state).
- **After Dose 4:** There are 1.875 doses in the body, then half is eliminated to leave 0.9375 doses (94% steady state).
- **After Dose 5:** There are 1.9375 doses in the body, then half is eliminated to leave 0.96875 (97% steady state).

At 97% we're considered to be at approximate steady state, where the rate of input equals the rate of elimination at one dose per dosing interval.

How do you calculate the average steady-state concentration?

Unfortunately, it's not as easy as counting chocolates in a box; there are many formulas that are used to calculate various pharmacokinetic parameters—and from there, the average steady-state concentration. But a very simple way to remember it is that the average C_{ss} is the total exposure (AUC) over one dosing interval divided by the duration of the dosing interval.

Can the loading dose speed up the time to steady state?

For a drug with a short half-life, steady state is achieved pretty quickly. But say you have a drug with a long half-life, and a patient who needs to achieve a therapeutic effect fast—for example, a critical care patient who needs antibiotics. How can you get that effect without having to wait days or weeks?

The bad news is that it always takes the same amount of time to achieve steady state: Four to five half-lives. The good news is, you can still **achieve a therapeutic effect** more quickly with a [loading dose](#). A loading dose is a higher dose administered on treatment initiation. It will still take the usual four to five half-lives to reach steady state, but the initial concentration will be closer to the eventual steady-state concentration—which means the therapeutic effect will happen faster.

What affects average steady-state concentration?

Steady-state concentration can fluctuate depending on many factors. Let's talk about three of the main ones:

1. DOSING INTERVAL

The dosing interval affects steady-state concentration in a proportional way. The more frequently the drug is given, the higher the steady-state concentration values.

2. DOSE

In the same way, higher doses will increase the C_{ss} values, and lower doses will decrease them. The dose required to reach and maintain steady state depends on the drug clearance rate, which in turn can be affected by the patient's demographic.

3. DRUG CLEARANCE

Drug clearance (CL) dictates the rate at which a drug is eliminated from the body. The slower the clearance, the more of the drug will remain in the system and the higher the C_{ss} (and vice versa).

Demographic factors can alter a patient's drug clearance rate, which then changes the C_{ss} . A patient's weight, their excretory and metabolic functions, and other drugs they're taking can all cause fluctuations. For example, say someone has renal failure. When they're administered a drug that's eliminated mostly via the kidneys, the steady-state concentration of that drug will be higher than it would be for someone with healthy renal function who's getting the same dosage.

How does steady state apply to drug studies?

In studies conducted in special populations, and in studies for assessing drug interactions, you might be required to take any necessary measurements when drug concentrations have reached steady state.

Understanding steady state is also important for choosing the right dose and dosing interval to achieve a desired steady-state concentration—and for determining how long it will take for therapeutic exposures to be achieved during repeat or continuous dosing, since it might take several doses for a drug to achieve therapeutic benefit.

Conclusions

A good understanding of steady state is helpful since this value is key in certain drug studies. These concepts are also critical in selecting an appropriate dose and dosing frequency to achieve safe, therapeutic drug concentrations in patients.

Steady-state concentration can be affected by various factors, from the patient's weight to the frequency of doses, and while you can speed up the therapeutic effects of a drug with a loading dose, you can't speed up the time to steady state.

Do you have more questions about how steady-state concentration is used in drug studies? [Contact us](#) today to speak with one of our senior consultants.

Contact us today:
888.615.5111 | discover@nuventra.com

