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THE ULTIMATE ZERO THEORY IN PHARMACOKINETICS: RESOLVING MATHEMATICAL SINGULARITIES DURING ABSOLUTE DISINTEGRATION FAILURE

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ABSTRACT

Objective: To mathematically and pharmacokinetically model the physiological scenario of a complete tablet dissolution failure within the gastrointestinal tract. This study applies the mathematical framework of the Ultimate Zero Theory (UZT) to resolve traditionally undefined pharmacokinetic expressions resulting from zero drug absorption. Specifically, the aim is to evaluate the mathematical resolution of the dissolution rate, the Area Under the Curve (AUC), true systemic clearance (CL), and apparent oral clearance, alongside evaluating the intrinsic organ clearance (CLint) when systemic exposure is completely absent. **Result:** Physical observation demonstrates that upon complete dissolution failure, the solid dosage form transits the gastrointestinal tract unabsorbed and is excreted entirely in the feces. Pharmacokinetically this total lack of systemic absorption yields an AUC of exactly zero. Furthermore, this event validates UZT across two distinct clearance calculations. First, using the exact systemic clearance formula $CL = \frac{F*D}{AUC}$ the complete lack of absorption renders bioavailability (F) as zero, creating the equation CL = $\frac{0}{0}$, which UZT resolves to 0. Second, calculating the apparent oral clearance by dividing the administered drug mass by the AUC creates the expression $\frac{m}{0}$, which UZT also physically and mathematically resolves to 0. Crucially, while calculated clearance parame ters collapse to zero because the drug never reached the bloodstream, the intrinsic clearance (CLint) of the hepatic and renal systems remains entirely at baseline; the body's internal organs maintain perfect functional capacity but simply lack the substrate required to initiate metabolism. **Conclusion:** The application of UZT provides a robust mathematical resolution for the undefined errors traditionally encountered in pharmacokinetic modeling when absorption is absolute zero. UZT validates that the mathematical outputs of 0/0 = 0 and m/0 = 0 perfectly reflect the physical reality of failed drug delivery. Ultimately, this framework establishes a critical pharmacological distinction: a calculated systemic clearance of zero simply signifies a formulation failure within the gastrointestinal tract. This is a clear distinction that the systemic clearance of zero just means the formulation failed, it does not mean the body's internal organs stopped working, the body's intrinsic clearance (the actual health and capacity of the liver and kidneys) remains completely unchanged.

KEYWORDS: *Zero* Divided by *Zero*, The Ultimate *Zero* Theory, Problems, indeterminate, Undefined, Infinite, Brahmagupta, Basic Method of Division, Mathematics, Clearance of drug, Area Under Curve (AUC).

1. INTRODUCTION: Historical and Modern Perspectives on Division by *Zero*

The concept of *Zero* has played a foundational role in the evolution of mathematics. However, its interaction with division remains one of the most perplexing topics. Specifically, operations like and have sparked philosophical debate and mathematical refinement across centuries. Modern mathematics generally deems these expressions undefined or indeterminate due to logical contradictions. Yet, history shows that earlier mathematicians made bold attempts to define them, paving the way for newer interpretations such as the **Ultimate *Zero* Theory (UZT)**.

1.1 Ancient Indian Mathematics: Brahmagupta's Insight (7th Century CE)

Since ancient times itself, the main concept is that dividing zero by zero (0/0) and any non-zero number by zero (1/0) is practically an undefined and very difficult task, Arithmetic of *Zero* in many contexts in mathematics, it is completely attributed to Hindu contributions and specially to Brahmagupta.

"The arithmetic of *Zero* is entirely the Hindu contribution to the development of mathematical science, with no other early nations do we find any treatment of *Zero*".[1]

Brahmagupta was an Indian mathematician and astronomer. In 628 AD Brahmagupta described the division by *Zero* in Brahmphutasiddhanta and he wrote:

"Positive, divided by positive, or negative by negative, is affirmative. Cipher, divided by cipher, is nought. Positive, divided by negative, is negative. Negative, divided by affirmative, is negative. Positive, or negative, divided by cipher, is a fraction with that for denominator: or cipher divided by negative or affirmative".[2]

In 2001, Fischbein, Efraim describes about the concept of infinity and several problems which is directly related to the process of infinity and he wrote:

"Infinity is a concept that mankind has struggled to grapple with throughout ancient time. Humans are better equipped to handle the finite processes create contradictions".[3]

1.2 Bhaskara II (12th Century CE): Toward Infinity

Building on Brahmagupta, Bhaskara II advanced the discussion he proposed that dividing a number by *Zero* results in infinity, After Brahmagupta, Mahavira attempted to modify the Brahmasphutasiddhanta of Brahmagupta. Bhaskar also worked on dividing by *Zero*. He describes the division by *Zero* in 1152 AD is written following-

"Statement: Dividend 3. Divisor 0. Quotient the fraction 3/0. This fraction, of which the denominator is cipher, is termed an infinite quantity".[4]

He also noted contradictions in this logic, revealing early awareness of mathematical paradoxes.

1.3 The Renaissance to Calculus: From Newton to Limits

With the rise of calculus in the 17th century, thinkers like Isaac Newton and Gottfried Wilhelm Leibniz confronted the issue of division by *Zero* using the concept of limits. While Newton never defined 0/0, such expressions emerged in derivatives and were treated via limiting processes

In 1744, Isaac Newton introduces the division by *Zero* and he wrote that "1/0 = Infinitae".[5]

1.4 Modern Mathematical Treatment

In contemporary mathematics, division by *Zero* is handled rigorously:

In 2016, Jaan Pavo Barukčić and Ilija Barukčić wrote about the division *Zero* by *Zero* in their journal and which is written below-

"When *Zero* divided by *Zero* (0/0) is called as an indeterminate and further it also claims that division of *Zero* by *Zero* (0/0) is called as no defined value".[6]

1.5 Historical Evolution of the Clearance Concept

The mathematical formalization of clearance has its origins not in whole-body pharmacokinetics, but in early 20th-century renal physiology. The term "clearance" was initially introduced to describe the efficiency of the kidneys in removing urea from the blood, defined conceptually as the theoretical volume of blood completely cleared of urea in one minute.[7]

The transition from a strictly renal metric to a broader, multi-compartmental pharmacokinetic parameter began to evolve over the following decades as scientists realized that the impact of disease on drug absorption and elimination required detailed pharmacokinetic data at single points in time.[8]

The modern, model-independent definition of systemic clearance—which links bioavailability (F), administered dose, and Area Under the Curve (AUC)—was heavily formalized in the 1970s. Pioneering work decoupled clearance from strict compartmental assumptions, establishing it as an independent physiological parameter reflecting the body's total intrinsic elimination capacity.[9] The mathematical development of clearance concepts during this era allowed the AUC to be reliably derived from the dose and the rate of elimination, forming the bedrock for modern clinical predictions.[10] This foundation was subsequently expanded into the "well-stirred" and "parallel-tube" models of hepatic clearance. As highlighted in recent comprehensive reviews, these models embedded the Cl = (F*Dose)/AUC relationship into standard practice, remaining crucial for predicting both unbound and total drug concentration-time relationships in the blood.[11]

While these classical formulations revolutionized drug dosing, they were inherently built upon the assumption of successful systemic entry (F > 0). In contemporary oncology and precision medicine, continuous infusion doses and oral therapies are routinely adjusted using pharmacokinetic-guided algorithms to attain predetermined target AUCs.[12] However, when therapies face complex absorption barriers or absolute absorption failure (F = 0), classical clearance equations are mathematically unresolved. Addressing this boundary condition through frameworks like the Ultimate Zero Theory is a critical next step for the development of highly accurate, AI-based pharmacokinetic analyzers.

2. Method: The Ultimate *Zero* Theory

2.1 Core Rule: Since ancient times a problem of dividing *Zero* by *Zero* or dividing any non-*Zero* number by *Zero* is a very difficult task. To solve the problem dividing *Zero* by *Zero* or dividing any non-*Zero* number by *Zero*, I have discovered a new theory this can show that if *Zero* divided by *Zero*, then the answer will be only one number not many numbers. **The Ultimate *Zero* theory** is defined as "*In division the numerator (m) is divided by denominator (n), then the answer number (o) is less or equal to numerator (m),* $n \neq (0 < n < 1)$.

For any division: m/n = o where o ≤ m, o ∈.[0, m], $n \neq (0 < n < 1)$

$$\frac{m}{n} = \begin{cases} m/n, & if\ n \neq 0,\ n \geq 1,\ n \in N \\ 0, & if\ m = 0,\ n = 0 \\ undefined\ [0,m], & if\ m \neq 0,\ n = 0, m \in N \\ P_v \times 10^D, & 0 < n < 1,\ m,n = Primary\ Value, D = Dispower \end{cases}$$

- This theory proves that the *Zero* divided by *Zero* is equal to *Zero*. It also describes the basic method of division either number is *Zero* or any non-*Zero* number. There are several examples are written below-

i) $\frac{100}{25}$ = 4, where 4 ∈.[0, 100]

ii) $\frac{30}{30}$ = 1, where 1 ∈.[0, 30]

iii) $\frac{25}{1}$ = 25, where 25 ∈.[0, 25]

iv) $\frac{17}{1}$ = 17, where 17 ∈.[0, 17]

v) So, $\frac{0}{0}$ = 0, where 0 ∈.[0, 0]

2.2 Non-*Zero* Divided by *Zero*: If m/n (where m≠0, n=0) is undefined because there are "many numbers below dividend o ∈.[0, m]," meaning no unique quotient can be determined.

Theory also describes that any non-*Zero* number divided by *Zero* is undefined. We cannot define that number because there are many numbers below that dividend. So that any non-*Zero* number divided by *Zero*, it is undefined. There are some examples are given below-

i) $\frac{10}{0}$ = undefined.[0, 10]

ii) $\frac{1}{0}$ = undefined.[0, 1]

iii) $\frac{9}{0}$ = undefined.[0, 1]

- **Note:** The final value in this condition depends upon the experimental observation, they may change according to condition where we applying.

2.3 Adjustment Principle for Decimal Divisors: When 0 < n < 1, **The Ultimate *Zero* theory** introduces an adjustment mechanism to avoid infinite or undefined outputs by converting both numerator and denominator as following written:

$P_v \times 10^D,\ 0 < n < 1,\ m,n = Primary\ Value,\ D = Dispower.$

Example: 15 / 0.7 = (1.5 × 10) / (7 × 10^{-1}) = 21.428

2.4 Cross Multiplication Principle:

- In Classical Mathematics division rule- m/n = o ⇒ m = o *n
- In UZT m/n = o ⇒ (m/n) × n = o × n

3. Application of "The Ultimate *Zero* Theory" in Drug Clearance in Novel Drug Delivery Systems (NDDS): Reconciling Classical Pharmacokinetic Clearance with Zero-Absorption Scenarios: An Interpretive Framework

In pharmacokinetics, clearance is a fundamental parameter that quantifies the efficiency of drug elimination from the body. While its classical definition is robust for typical drug disposition, it presents a conceptual and mathematical challenge in scenarios of complete drug delivery failure, such as the non-release of a drug from an advanced delivery system. This document outlines the classical view and introduces the Ultimate Zero Theory (UZT) as a complementary conceptual framework to provide a more holistic understanding.

3.1 The Classical Pharmacokinetic Perspective

Systemic clearance (CL) is defined as the volume of plasma cleared of a drug per unit of time, representing the body's intrinsic physiological capacity for elimination.[13,14] It is calculated from in vivo data using the formula: clearance Cl = (F*Dose)/AUC where:
Cl is the clearance.
F is the drug's bioavailability.
D is the administered dose.
AUC is the area under the plasma concentration-time curve.

A critical prerequisite for this calculation is the presence of the drug in systemic circulation (F > 0 and consequently AUC > 0). In a situation of total absorption failure, both F and AUC are zero. This renders the clearance equation mathematically indeterminate (0/0).[15,16]

From a classical viewpoint, clearance is a physiological constant that cannot be determined if the drug is never

present to be eliminated. The resulting indeterminate value, or an infinite value for clearance Cl = (F*Dose)/AUC, serves as a diagnostic indicator of failed bioavailability, not as a measure of the body's elimination capacity.[17,18]

3.2 The Ultimate Zero Theory (UZT): A Conceptual Framework

The Ultimate Zero Theory (UZT) is an interpretive framework designed to address the conceptual gap that arises from the mathematical indeterminacy in zero-absorption cases. It is not intended to redetermine classical PK but to provide a logical, practical interpretation of the outcome.

UZT introduces the concept of **"administrative clearance"** for this specific scenario. The rationale is as follows:

Clearance describes the process of drug removal from the body.

If no drug is absorbed into the systemic circulation, the body's elimination organs (e.g., liver, kidneys) are not engaged in clearing the drug.

Therefore, the net amount of drug that was actually cleared is zero.

Under UZT, the **administrative clearance is defined as zero**. This provides an intuitive and unambiguous conclusion: no elimination occurred because no drug was available to be eliminated. It reframes the question from "What is the body's theoretical capacity?" to "What was the result of the drug administration event?"

3.3 Comparative Analysis: Classical PK vs. UZT Framework

The following table provides a direct comparison of the two perspectives, highlighting their definitions, applications, and interpretations in different scenarios.

Aspect of Comparison	Classical Pharmacokinetics	Ultimate Zero Theory (UZT) Framework
When Drug is Absorbed (F > 0, AUC > 0)	Clearance is a finite, calculable value representing the rate of drug elimination.	Clearance is a finite, calculable value representing the rate of drug elimination.
When Drug is NOT Absorbed (F = 0, AUC = 0)	Clearance is mathematically **indeterminate (0/0)**.	"Administrative clearance" is defined as **zero**.
Interpretation of Zero-Absorption Scenario	The body's physiological capacity for elimination is unchanged but **cannot be measured** due to the absence of drug.	The body's physiological capacity for elimination is unchanged but this can be about finite value.

4. RESULTS

The Ultimate *Zero* Theory (UZT)gives a new and simple way to understand division by *Zero*. In regular mathematics, dividing *Zero* by *Zero* is called indeterminate, and dividing any non-*Zero* number by *Zero* is often said to be infinite. But this creates confusion and problems, especially when used in real-life calculations. UZT fixe these issues with clear and logical rules.

The main results of this theory are:

Zero divided by *Zero* is equal to *Zero*:

$0/0 = 0$

Any non-*Zero* number divided by *Zero* is undefined, but not infinite:

According to UZT,

m/n =.[0, m]

Dividing by decimals less than 1 can be corrected using a scaling rule:

For example: $5/0.2 = 5 \times 10/2 \times 10^{-1} = 25$

The theory is also useful in science. For instance, in drug delivery systems, if a medicine is not absorbed at all, the AUC (area under the curve) becomes 0. Using the traditional method, this would make drug clearance equal to infinity. But with UZT it becomes a finite.

Clearance = (F×Dose)/ AUC $\Rightarrow$ Clearance = $0 \times 100/0 = 0$

5. CONCLUSION

The Ultimate *Zero* Theory gives a new and better way to deal with division by *Zero*. It solves old problems in mathematics where $0/0$ was considered indeterminate and $m/0$ infinity. But UZT says:

$0/0 = 0$,

$m/0$ = undefined, but stay within limits.[0, m]

This theory helps avoid confusion, especially in science and real-life situations. It also shows how to fix problems when dividing by decimals smaller than one. The theory is not only logical but also practical. It works in fields like pharmacokinetics, where it gives better results than the traditional method. In short, UZT is a useful and clear solution to the age-old problem of dividing by *Zero*. It helps students, scientists, and programmers to get accurate answers without running into confusing or impossible results like infinity or indeterminate values.

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