Developing and validating discriminatory and bio-relevant drug dissolution tests and profiles

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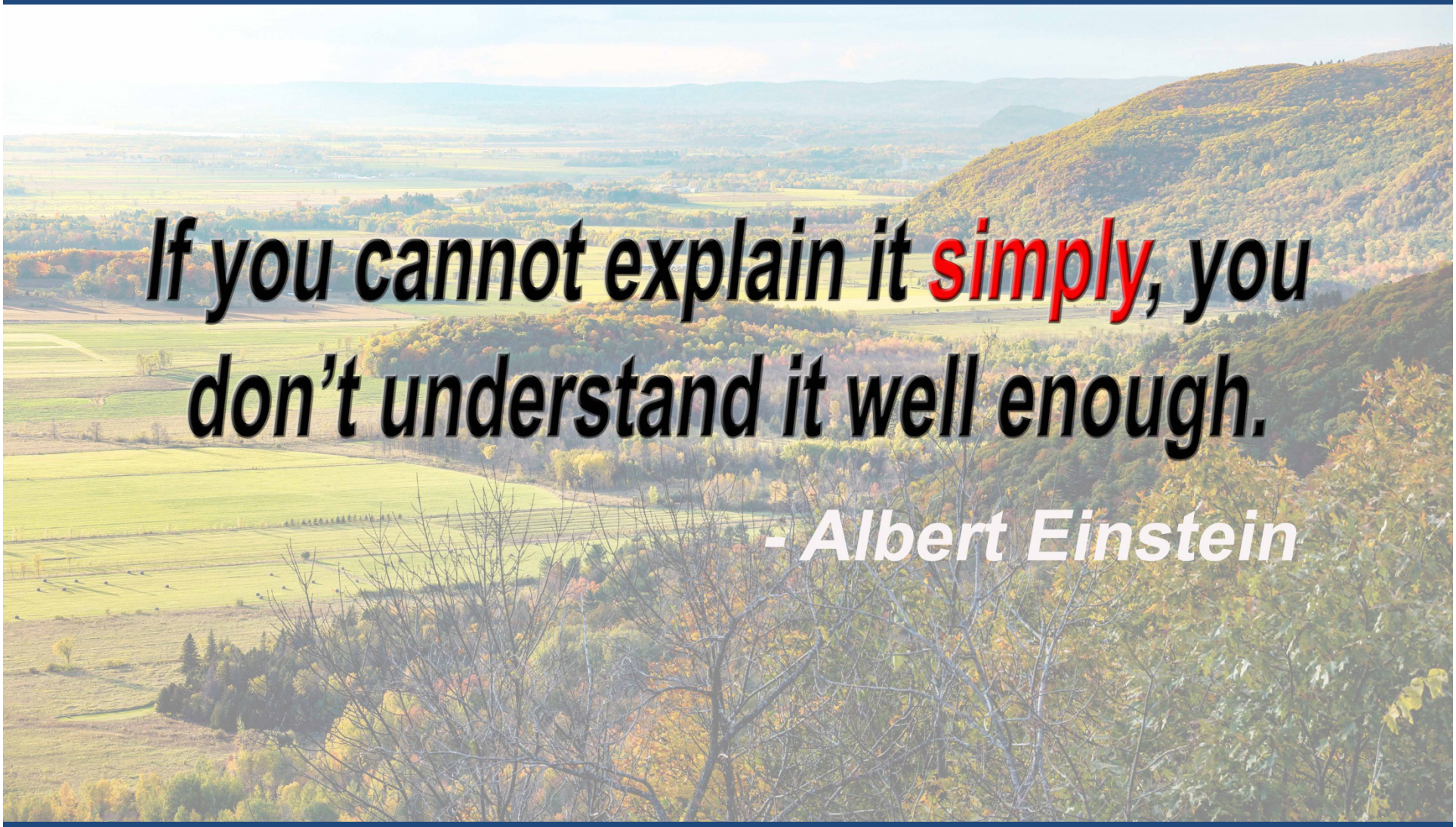
Relevant publication

Developing Discriminatory Drug Dissolution Tests and Profiles: Some Thoughts for Consideration on the Concept and Its Interpretation. *Dissolution Technology*, 2006.

Outline

- Defining a discriminatory & bio-relevant dissolution test
- Logical and scientific considerations
- Physiological expectations
- Developing and validating the test (selecting experimental conditions)
- Practical case studies of developing discriminatory tests



A discriminatory drug dissolution test?

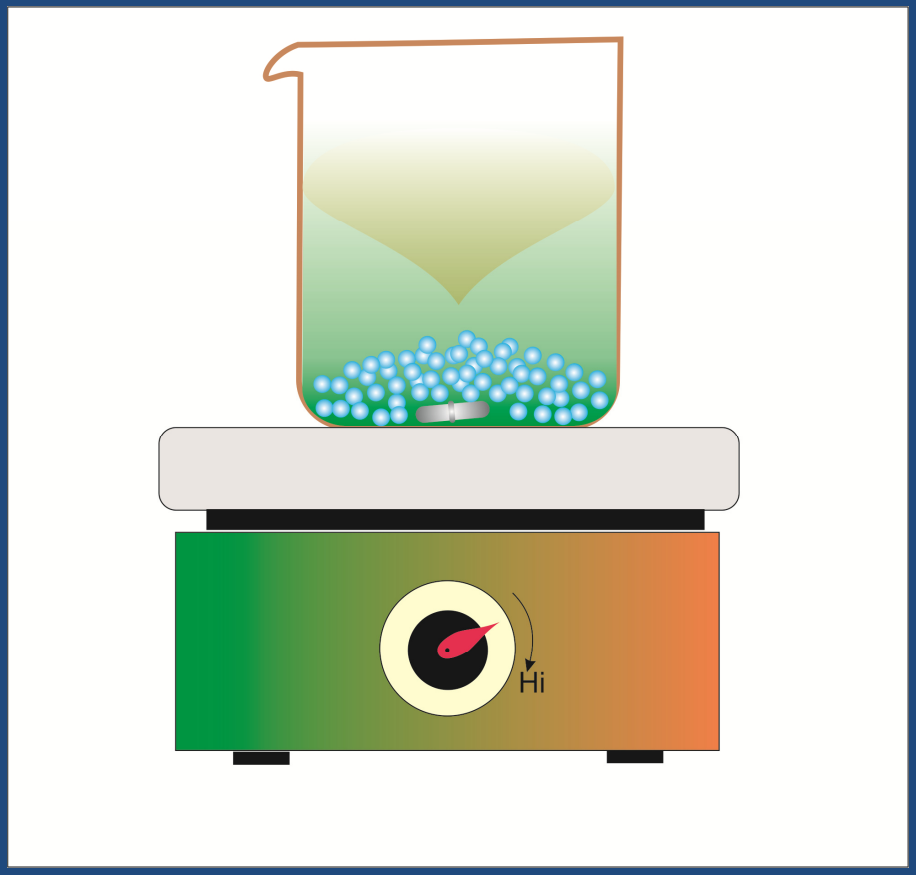
What is it and why we even need one?

But before that:
A drug dissolution test?

What is it and why we even need one?

Note that drug dissolution and drug release testing/test is one and the same thing, and I will be using both terminologies interchangeably.

A drug dissolution test/tester?

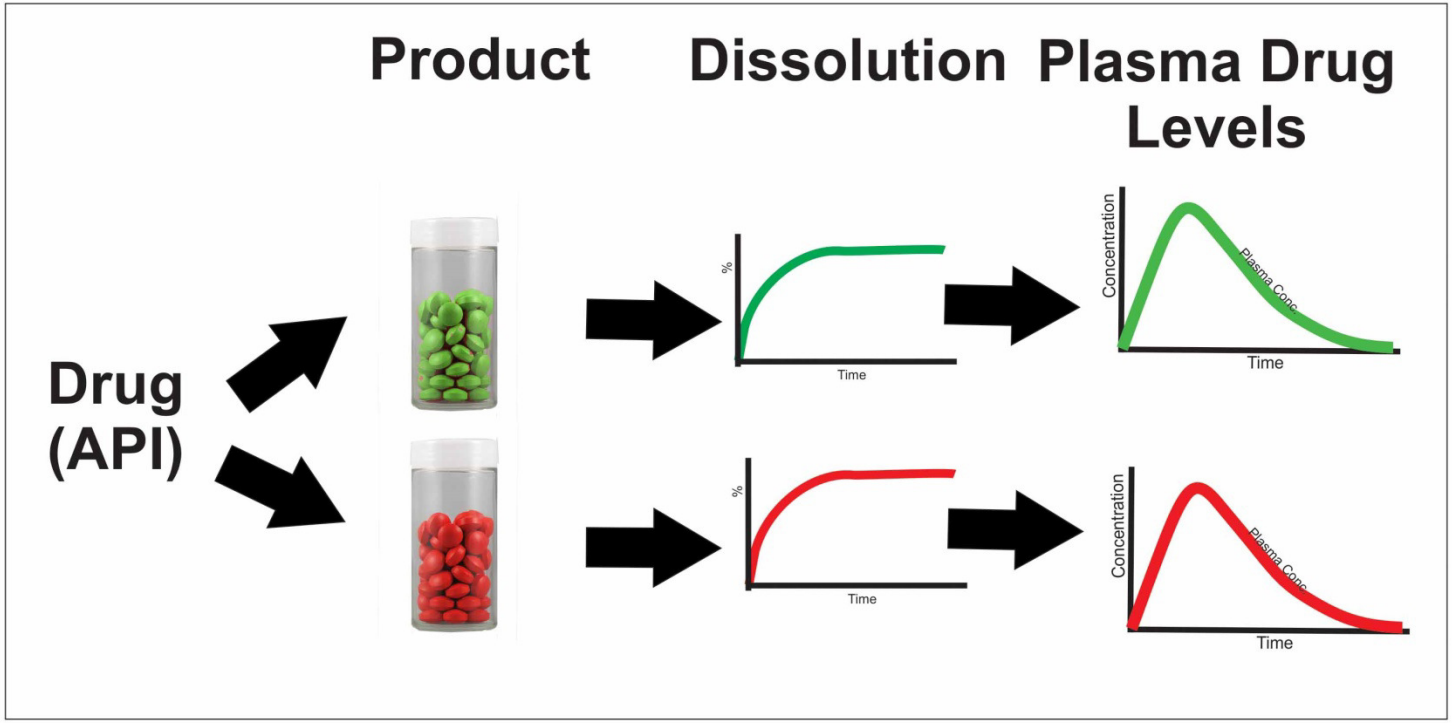


A drug dissolution test?

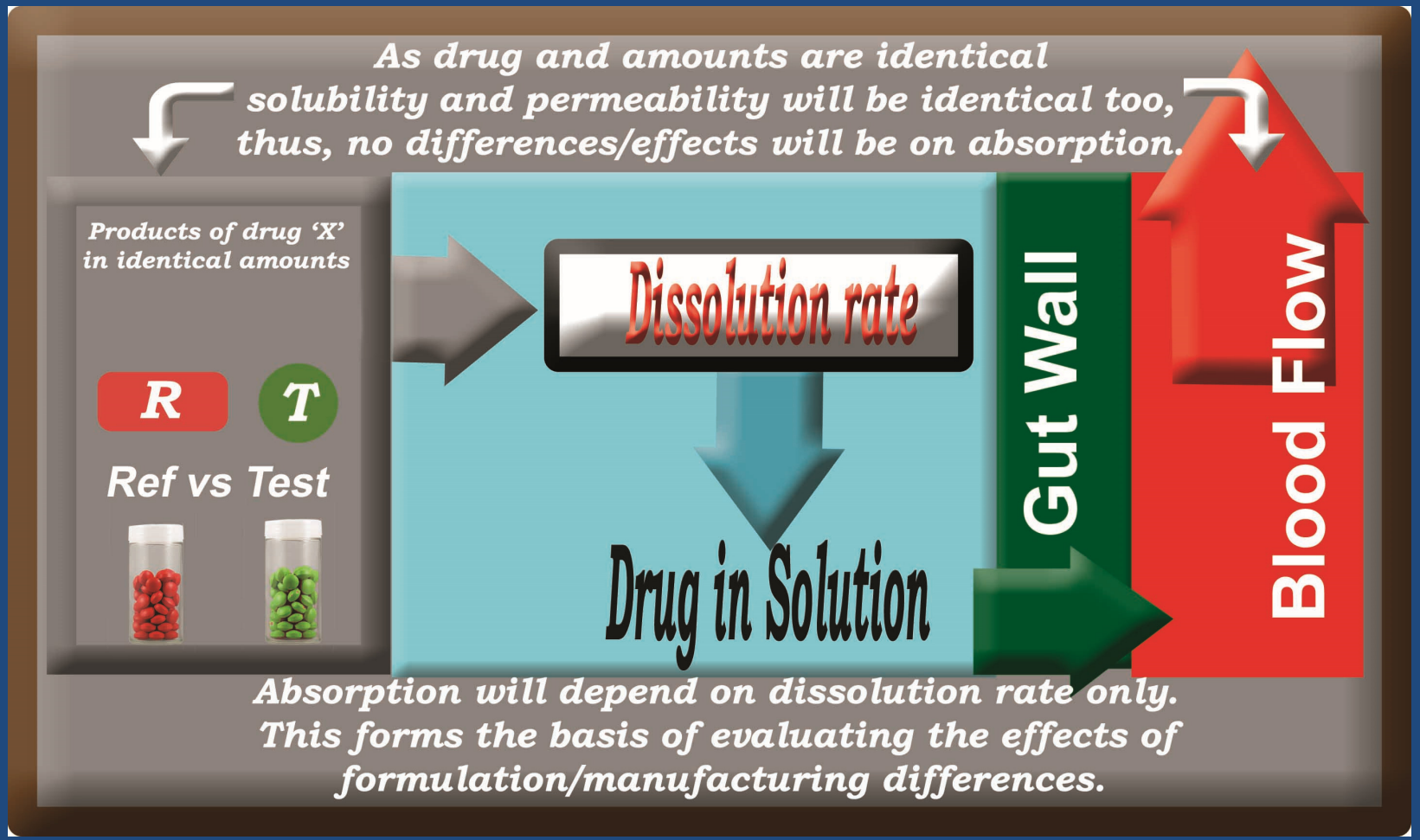
A test conducted to assess drug release characteristics of tablet/capsule products based on the following principle.

Therapeutic effects are dependent on plasma drug levels which in turn relate to drug release characteristic of the product in the GI tract.

Why Dissolution testing?



Why Dissolution testing?



Why drug dissolution testing?

(Product Quality Assessments)

Assessing the dissolution characteristics of the products in vivo, in particular GI tract, forms the basis of quality assessment of the products.

Why drug dissolution testing?

(Product Quality Assessments)

It is not a test to assess formulation or manufacturing differences or changes, but to assess impact of these differences or changes on in vivo drug dissolution/release.

Why drug dissolution testing?

(Product Quality Assessments)

To further emphasize the fact, if a dissolution test is not relevant to in vivo characteristics (i.e. bio- or clinically relevant), *it cannot be used as a quality control test as well*.

Pharmacopeial Dissolution Tests

USP categorically states that "Compliance with any of the [dissolution] tests does not assure bioequivalence or bioavailability" [USP 37, General Notices and Requirements]. Therefore, there is no point in using these tests as bio-relevant tests. One has to look somewhere else for bio-relevant tests.

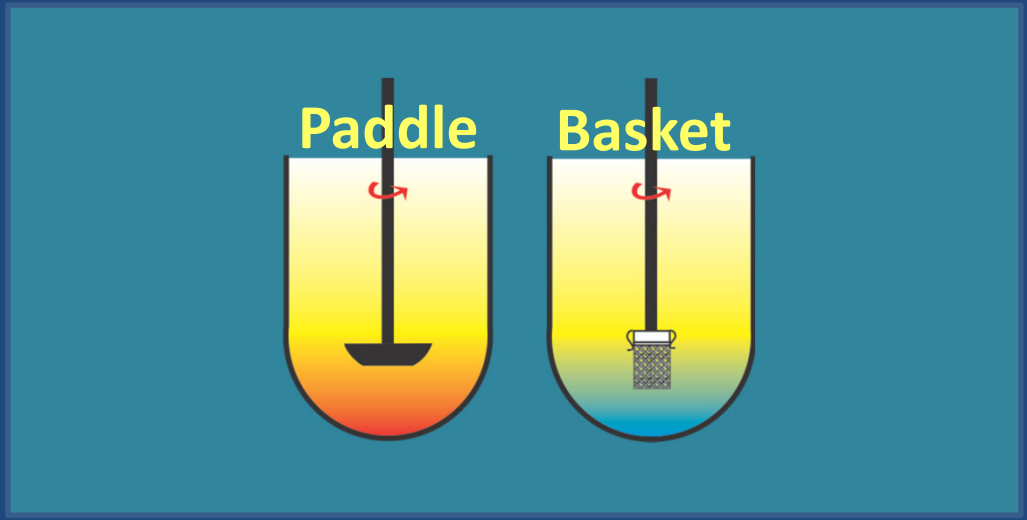
Dissolution Tests

The question is - why these are not bio-relevant tests (*what is the issue?*) and how to correct these? Because, until we have an appropriate dissolution test we cannot have a discriminatory dissolution test as well. *Period!*

First the Dissolution Testers

(Most commonly used ones)

Specialized beakers and stirrers known as -



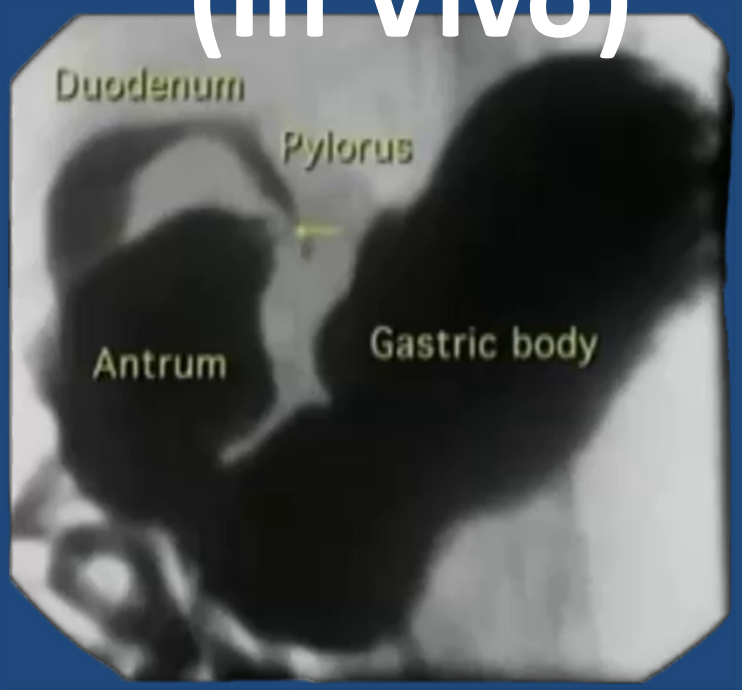
With rotation speed between 50 to 100 rpm – as per pharmacopeias e.g. USP

First the Dissolution Testers

(Most commonly used ones)

Physical/Mechanical Environment

(In Vivo)

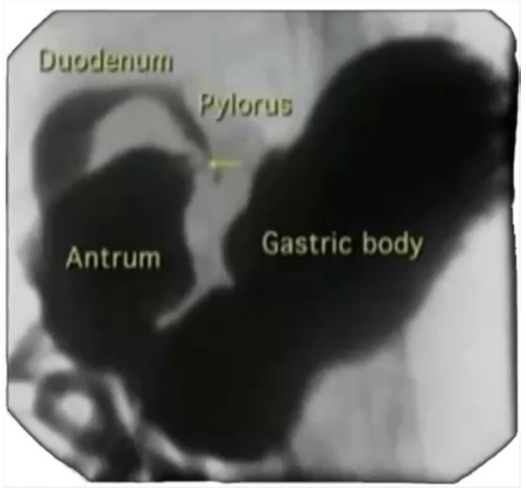


(In Vitro)

First the Dissolution Testers

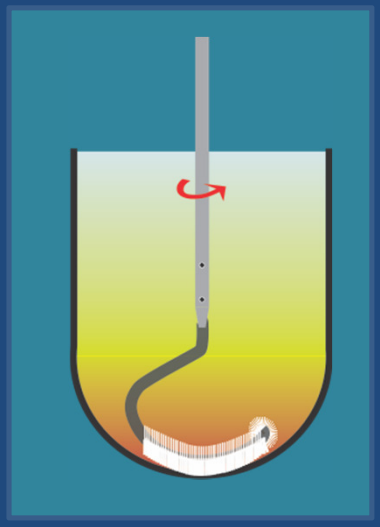
(Most commonly used ones)

Difference in environments



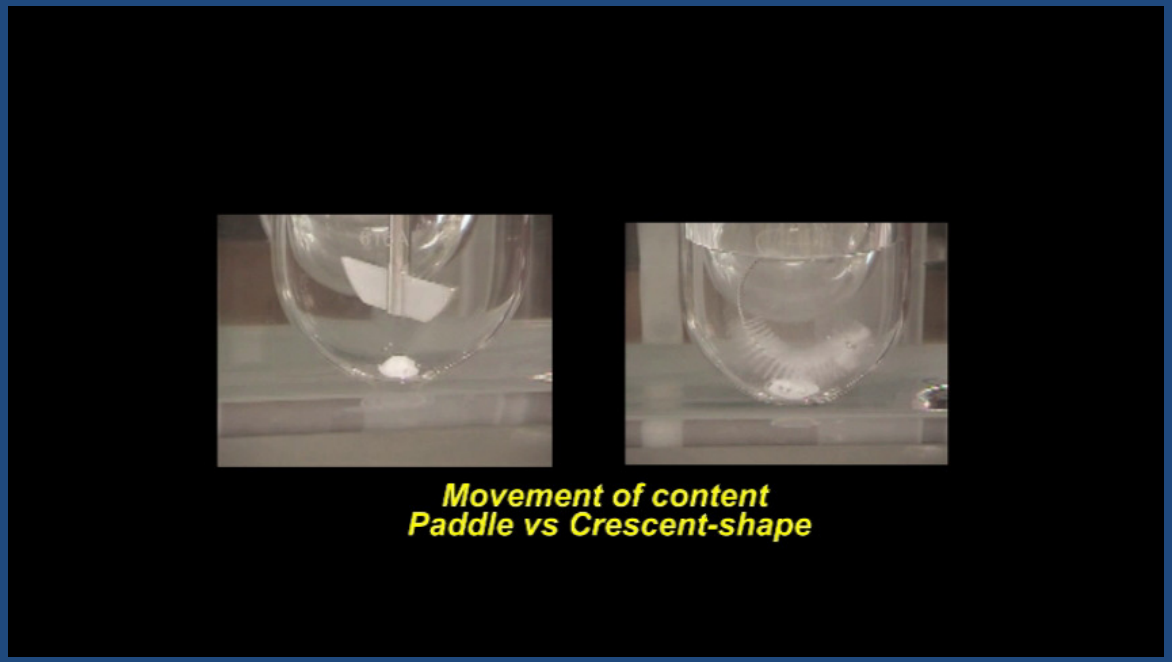
Source: Youtube

Modification of stirring



Crescent-shape spindle

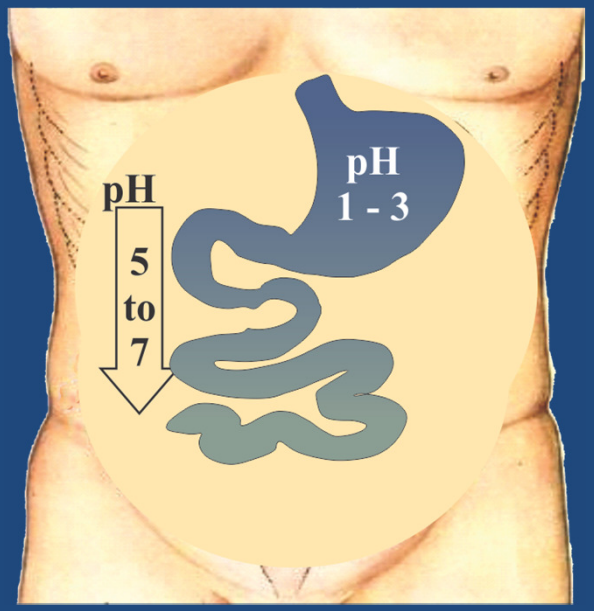
Modification of stirring



Crescent-shape spindle

Chemical Environment

(In Vivo)



Chemical Environment

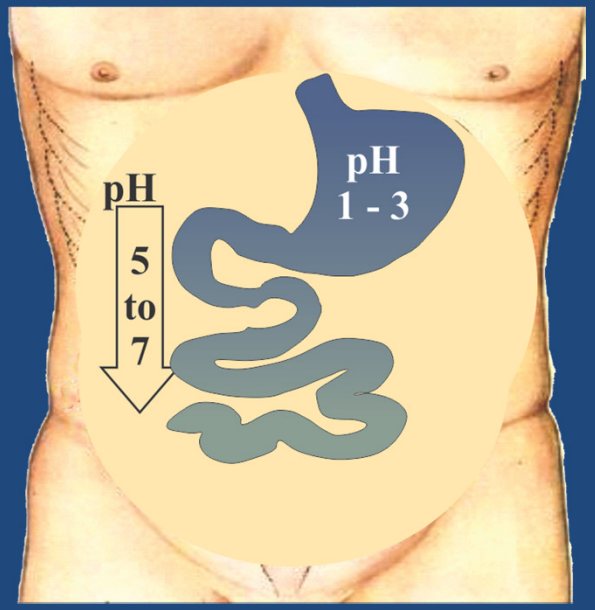
(In Vitro)

- Solvent (water or buffer)
- pH 1 to 6.8/7.2
- Volume: 500 mL to 2/4 L (with or without solubilizer)
- Stirring speed any rpm between 50 to 150
- Temperature: 37 ºC

Chemical Environment

(In Vitro)

Suggested choice of medium : **900 ml of water maintained at 37 ºC with stirrer (crescent-shape spindle) set at 25 rpm.**

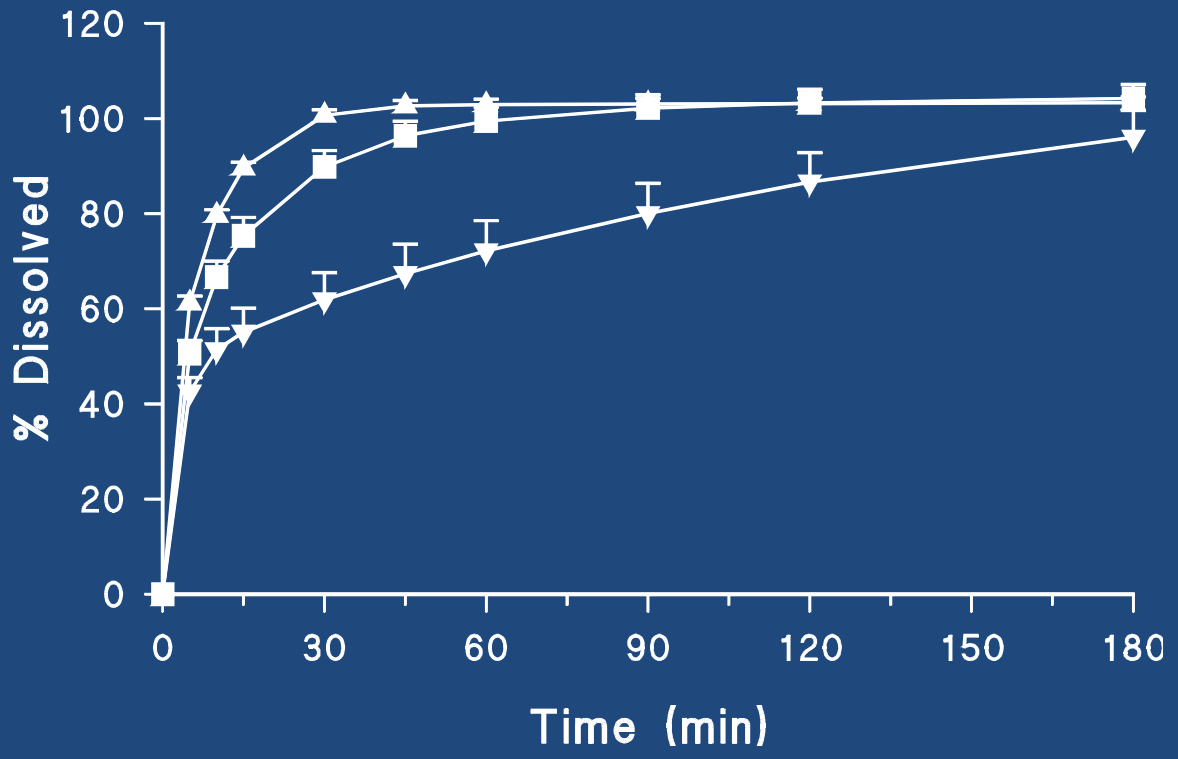


Bio-relevant dissolution testing requirements

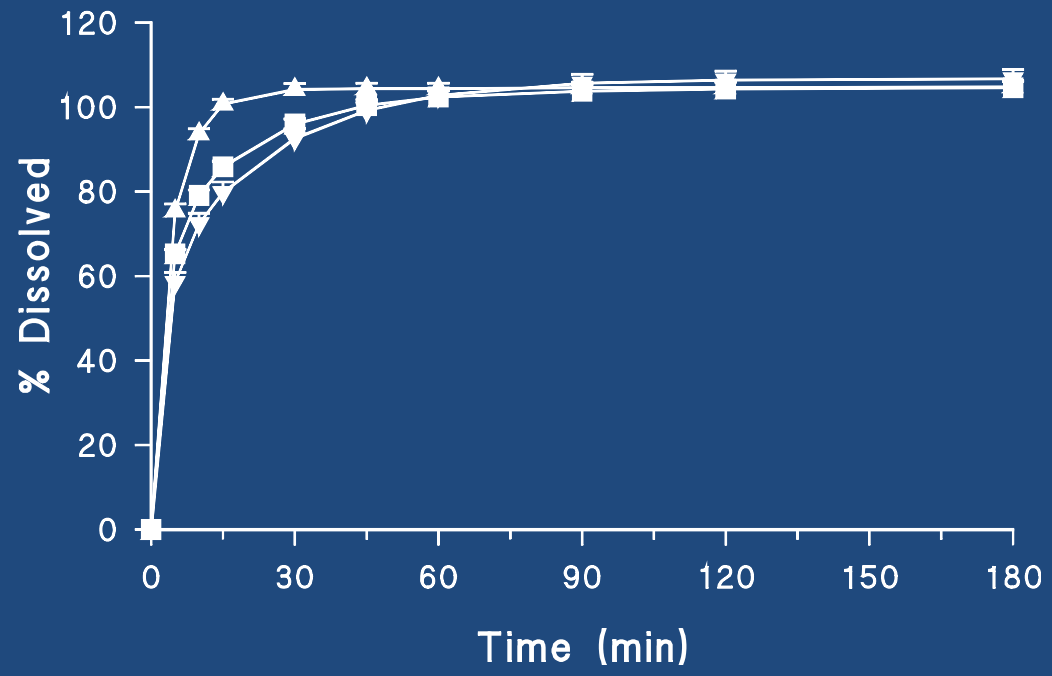
- **Efficient stirring and mixing**
- **Single set of experiments conditions**

As these requirements are not met using currently suggested testers/methods, one cannot obtain bio- or clinically relevant dissolution results.

Dissolution profiles of carbamazepine products products as per USP (Paddle) method



Dissolution profiles of carbamazepine products using crescent-shape spindle



Validation of dissolution method

A process of showing that a dissolution method is capable of providing expected (dissolution) results. This requires a product (i.e. reference product) with known dissolution characteristics established independently.

Validation of dissolution method

As there is no (reference) product available with known dissolution characteristics, it is *not* possible to validate a dissolution method, in the true sense/meaning of validation.

Validation of dissolution method

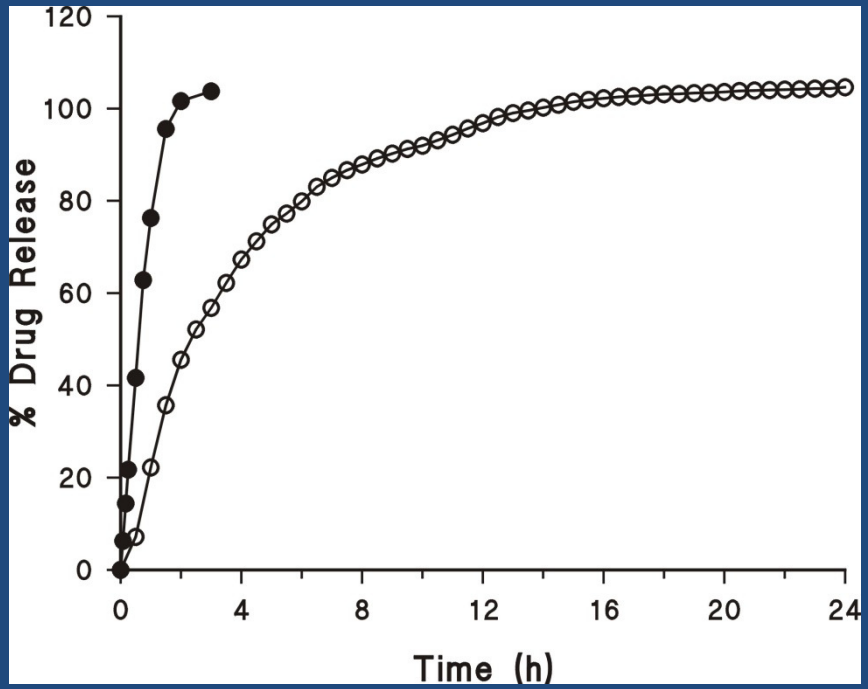
Claims of method developments and validations without using a reference product or with test products are simply scientifically invalid and such methods do not have any credibility or merit.

Validation of a dissolution method

In the meantime, I have suggested an approach based on relative drug release assessment.

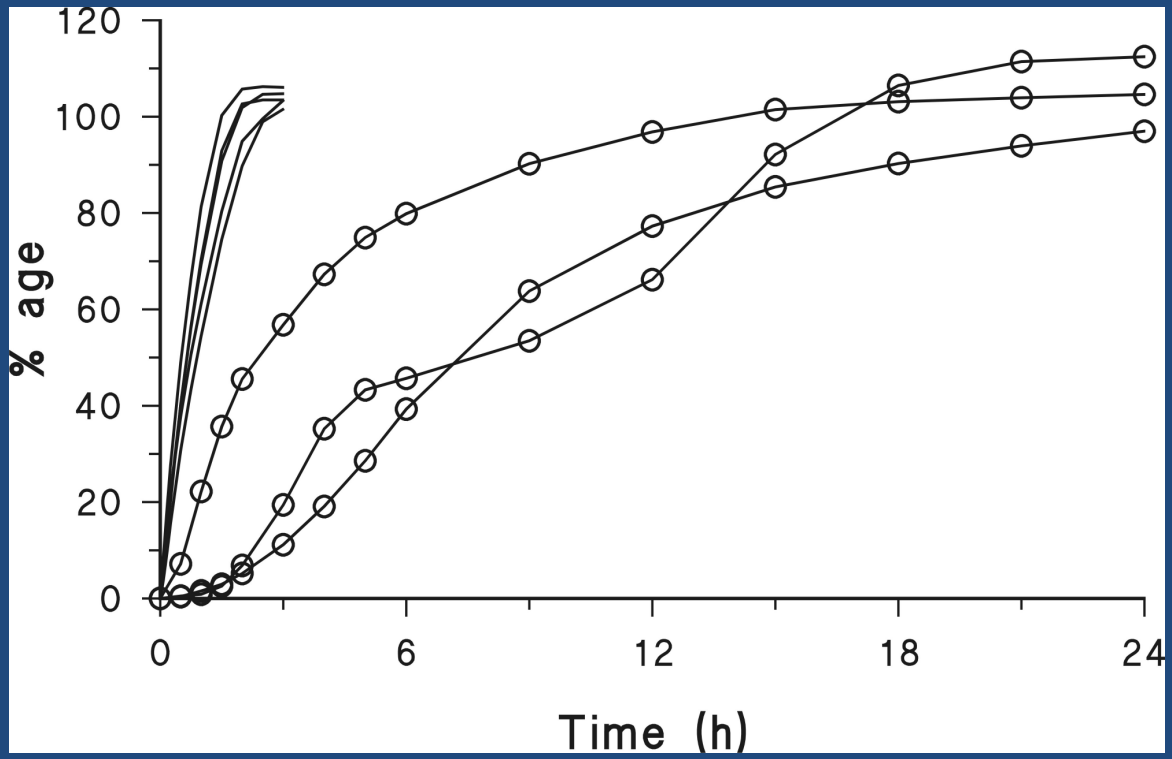
One can assess, validity or authenticity of a dissolution method by using products having two types of drug release characteristics *in humans*, such as IR and ER products.

Validation of a dissolution method



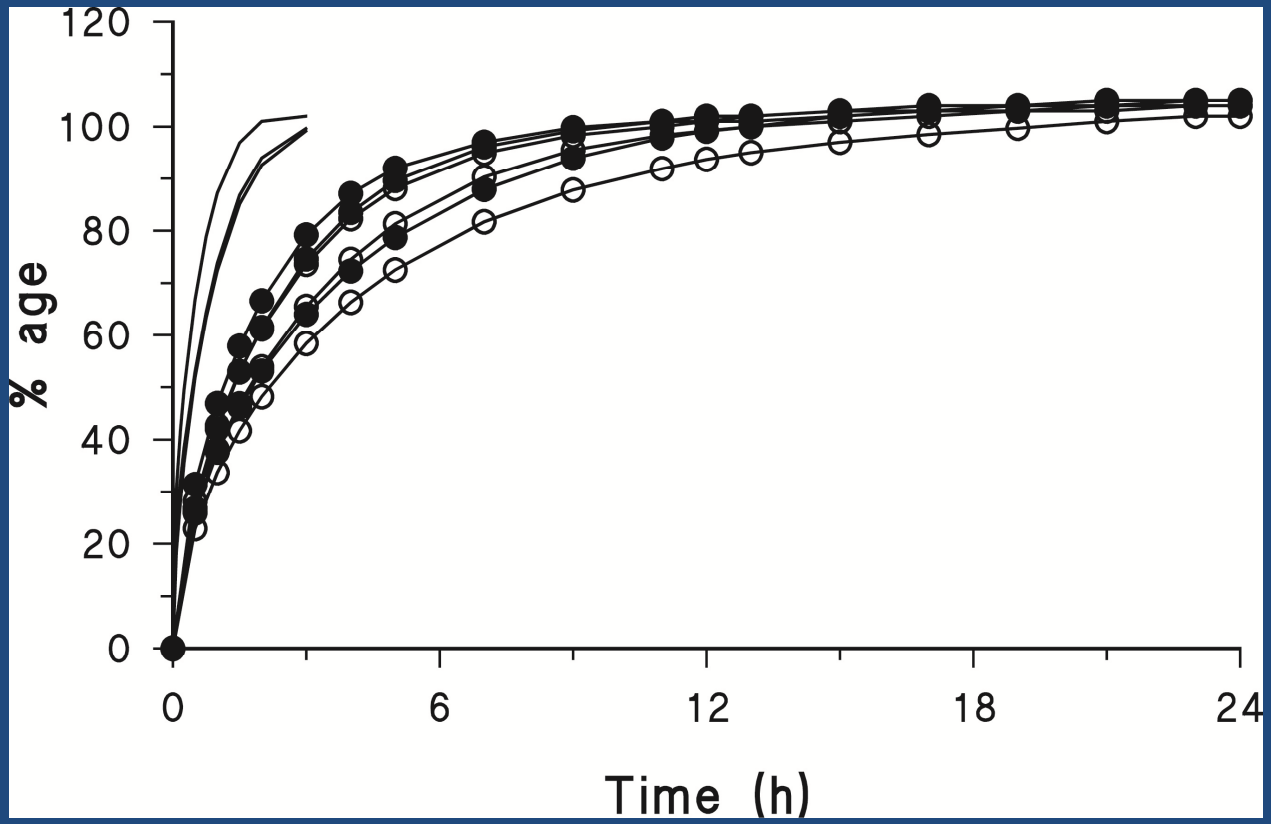
Dissolution profiles of diltiazem IR (solid circles) and ER (open circles) products in 900 mL of water maintained at 37 ºC using crescent-shape spindle set at 25 rpm.

Validation of a dissolution method



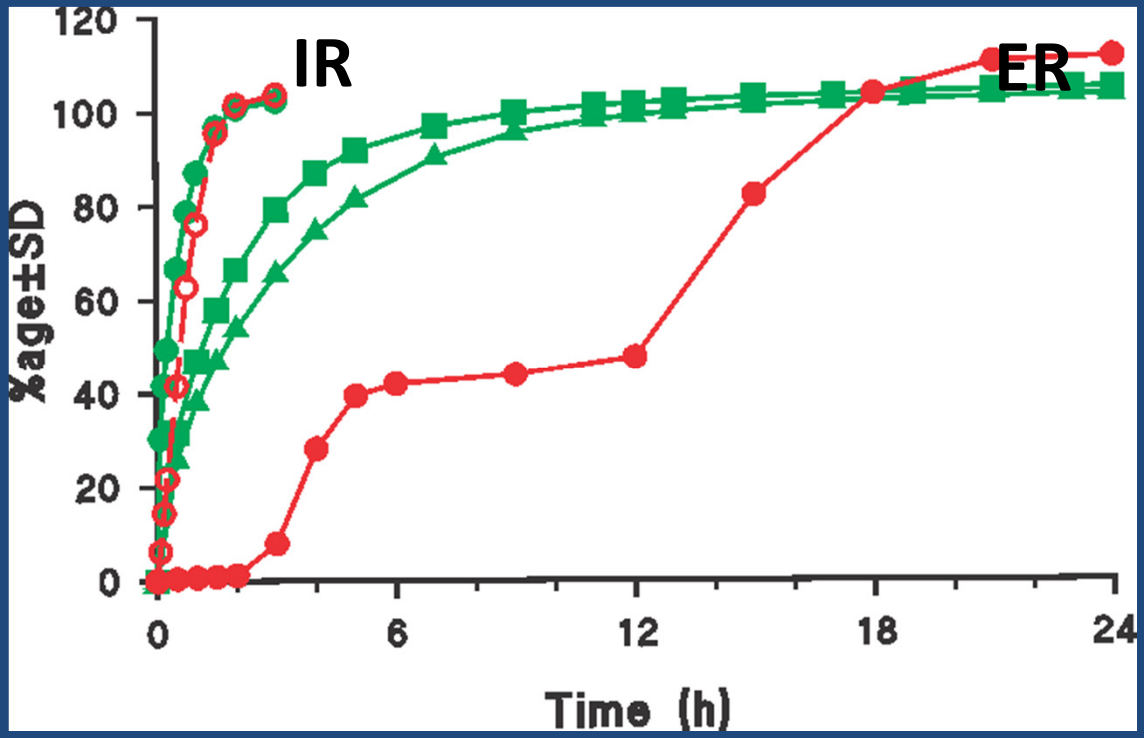
Dissolution profiles of multiple brands and types of *diltiazem* products with 900 mL of water maintained at 37 ^{o}C using crescent-shape spindle set at 25 rpm.

Validation of a dissolution method



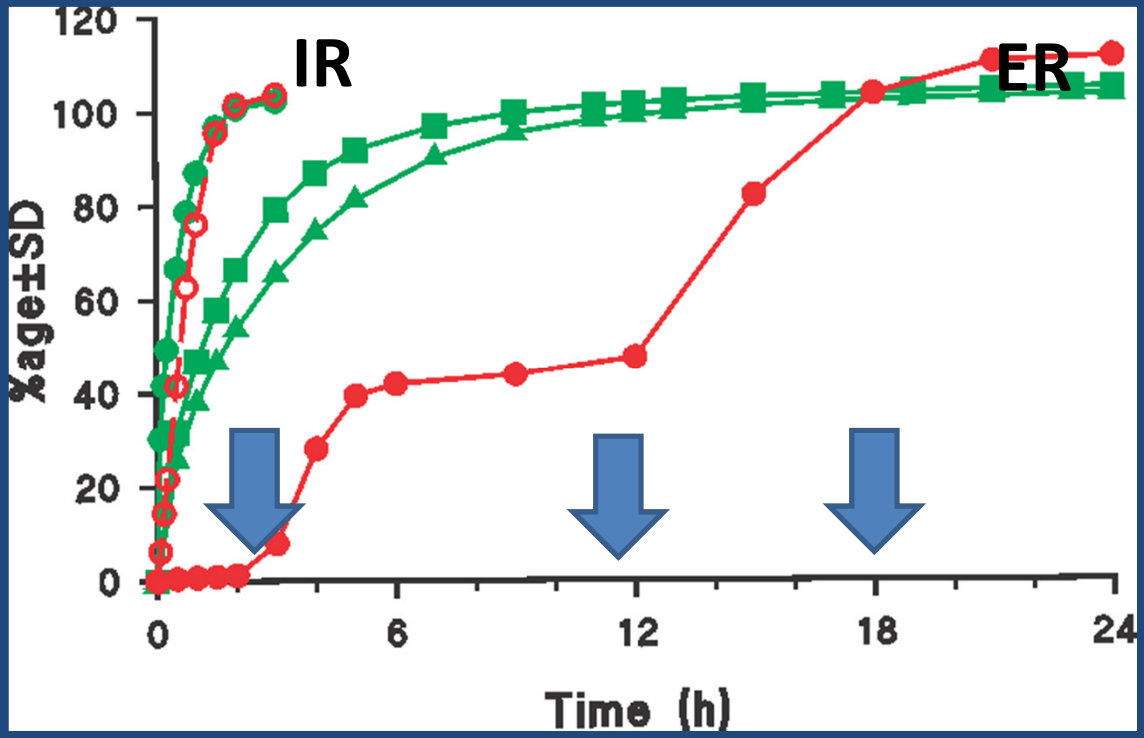
Dissolution profiles of multiple brands and types of *carbamazepine* products in 900 mL of water (+ 0.5% SLS) maintained at 37C using crescent-shape spindle set at 25 rpm.

Universal dissolution method



Diltiazem products (in red) and carbamazepine products (in green)

Selecting an RPM



Diltiazem products (in red) and carbamazepine products (in green)

Universal dissolution method

- APPARATUS: Vessel-based with crescent-shape spindle (set at 25 rpm)
- MEDIUM: 900 water (with or without solubilizer) maintained/ equilibrated at 37 ºC.

A dissolution method

(Have not discussed)

- Nature of API and/or formulation/manufacturing attribute
- Degassing/de-aerating of dissolution medium
- Analytical method (precision, accuracy, specificity etc.)

A discriminatory dissolution method

So now you have an appropriate dissolution method which needs to turn into a discriminatory method. *You don't.* It becomes a discriminatory method by itself. Let me explain.

A discriminatory dissolution method

A discriminatory dissolution method, or any method, is the one which is capable of differentiating good (acceptable) product from bad (unacceptable). In our case: a bio-relevant (good) vs non-bio-relevant (bad). Important thing to note here is that the test or tester does not tell if a product is good or bad, it just provide the test results. It is we (pharmacists, chemists, manufactures, regulators etc.) decide what is good or bad.

A discriminatory dissolution method

For example, we decide that if product(s) show dissolution characteristics of 80% or more dissolved within 60 minutes, then they will be considered acceptable (good) immediate release product(s). Any thing showing less than 80% dissolved will become unacceptable (bad) product. A dissolution method does not know these limits. It will only show the dissolution results.

A weighing scale analogy

A scale/test does not tell if the suitcase is heavy or light. It just tell the weight of the suitcase.

A discriminatory dissolution method

Similarly, ER products are required to dissolve following a specific pattern (profiles) in extended time period (usually more than 6 hr). If a product releases all its drug in less than 6 hours then it becomes an unacceptable (bad) product. A tester or method does not recognize whether it is dealing with an IR or ER product (good or bad). It just does its job of showing dissolution characteristics of the product. It is we who decide if the product is acceptable or not.

An important conclusion!

One does not require a discriminatory dissolution test/method but an appropriate (i.e. bio-relevant) one. An appropriate dissolution test by definition becomes a discriminatory test.

Another important conclusion!

If you need to measure weight, temperature, or pH of an item, you are provided, or use, a qualified and validated scale, thermometer or pH meter, respectively. You are not expected to develop these testers or established their discriminatory nature. Similarly, as an analyst, you should also receive a qualified and validated dissolution test/method. Developing and validating a discriminatory dissolution test, as a standalone exercise, is unnecessary practice and requirement, in particular using a test product itself.

www.drug-dissolution-testing.com

Summary

- A drug dissolution test is conducted to assess in vivo drug dissolution characteristics of a product. Without an in vivo link, a dissolution test has no useful purpose.
- A dissolution test can easily be conducted using a vessel containing 900 mL of water, w/wo solubilizer, maintained at 37 ^{o}C with soft but through mixing and stirring.
- An appropriate and valid dissolution test must be product and drug independent and capable of differentiating IR and ER products of a drug using the same experimental set.

Summary

- An appropriate and validated dissolution test by definition becomes a discriminatory test. There is no need to have extra steps or requirements.
- Industry and authorities should work on developing a reference product having established dissolution characteristics. Lack of availability of such a standard appears a major impediment in developing and simplifying appropriate (discriminatory, bio-relevant) dissolution tests.
- Availability of a standard/universal dissolution test and tester is a possibility and regulatory authorities and industry should explore this possibility to simplify drug dissolution testing, and by extension drug product developments.