Boštjan Petek
Scientific Advisor SGD
Sandoz

Beyond the Default High-Risk Label: Making Multiparticulate Extended-Release Capsules Predictable and Controllable

Evidence from Purposeful Formulation Variants, Predictive Dissolution, and Bioequivalence Studies



SANDOZ | lek

80 LET LEKA YEARS OF LEK

SANDOZ | lek

The high-risk label defines the starting question

For a coated multiparticulate ER generic, matching the RLD's in vivo performance requires control of formulation and process attributes that govern drug release.

01

Product and requirement

- Drug-loaded pellet cores with a protective sub-coat
- Release-controlling polymer film surrounds each pellet
- Pellets filled into hard gelatin capsules
- Generic must be bioequivalent to the RLD

02

Starting risk

- Starting risk assessment: high risk due to formulation-controlled release
- ER coating controls drug release
- Release may vary with materials and coating-process conditions

03

Development objective

- Understand the release mechanism and critical attributes
- Connect critical attributes and dissolution with systemic exposure
- Evaluate how deliberate release-rate changes affect systemic exposure

Can product understanding and clinically anchored evidence establish a stronger basis for predicting and controlling product performance?

SANDOZ | lek

Controlled release functions enabled purposeful test variants

ER-coating amount was deliberately varied to investigate the link between dissolution and systemic exposure.

WHAT WAS CONTROLLED

Coating functions

Film formation

Pore formation

Plasticization

Manufacturing functions

Pellet size, shape and size distribution

Protective sub-coat formation

Consistent release-film application

WHAT WAS DELIBERATELY VARIED

One deliberate change: ER-coating amount (% w/w)



Same material grades
Same relative coating composition
Same manufacturing platform

How do deliberate release-rate differences affect systemic exposure under fasting conditions?

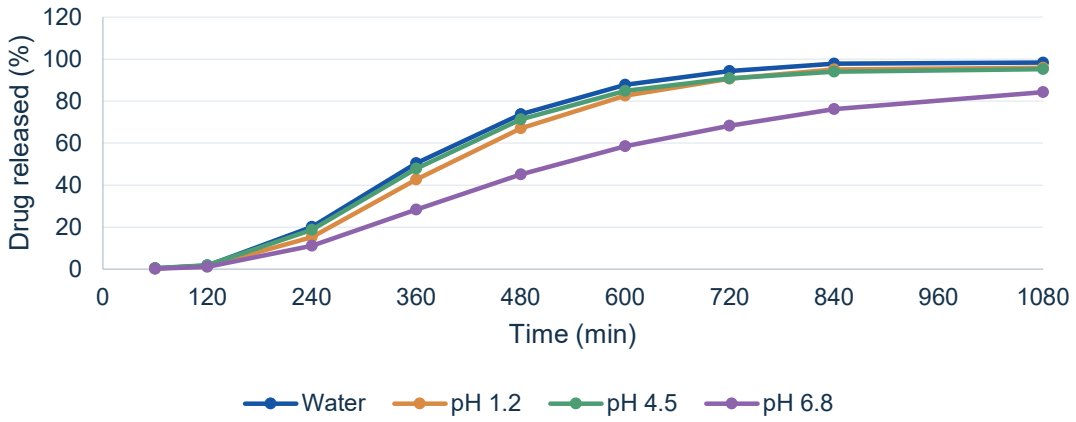
SANDOZ | lek

Dissolution sensitivity to medium and hydrodynamic conditions

The representative formulation is relatively robust to hydrodynamic changes, while dissolution medium materially affects dissolution.

Medium sensitivity

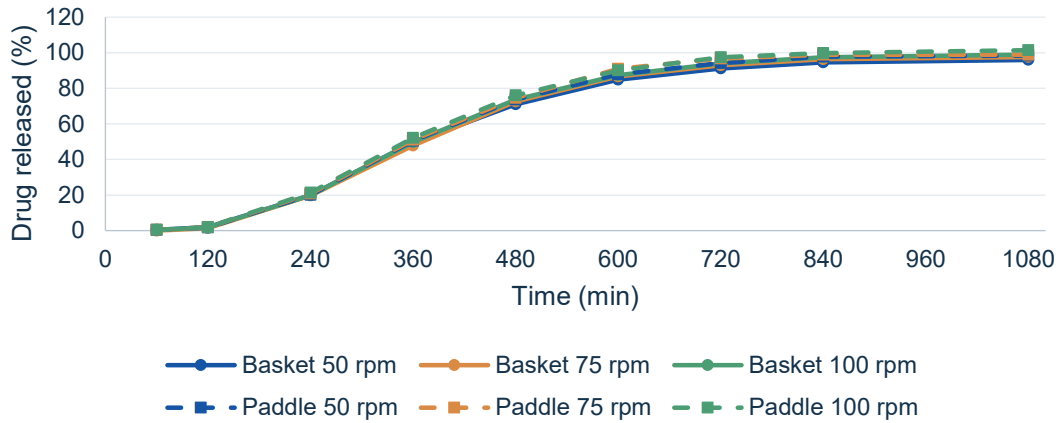
Apparatus 2, 50 rpm, 900 mL, 37°C



The release-controlling coating is designed to be pH-independent; lower drug solubility may contribute to slower dissolution at pH 6.8.

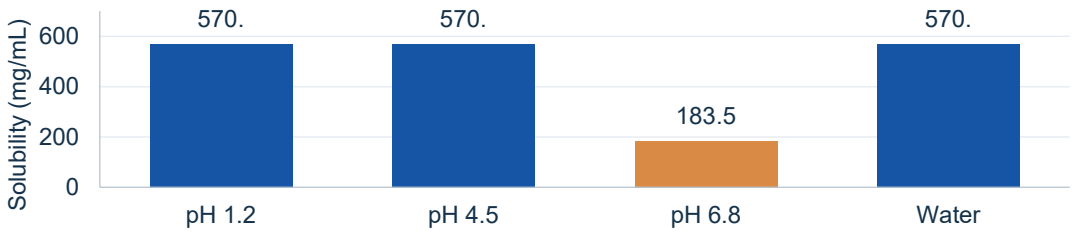
Hydrodynamic robustness

Water, 900 mL, 37°C



Release profiles were broadly similar across the tested apparatus and agitation speeds.

Solubility context: salt of a weak base



KEY TAKEAWAY

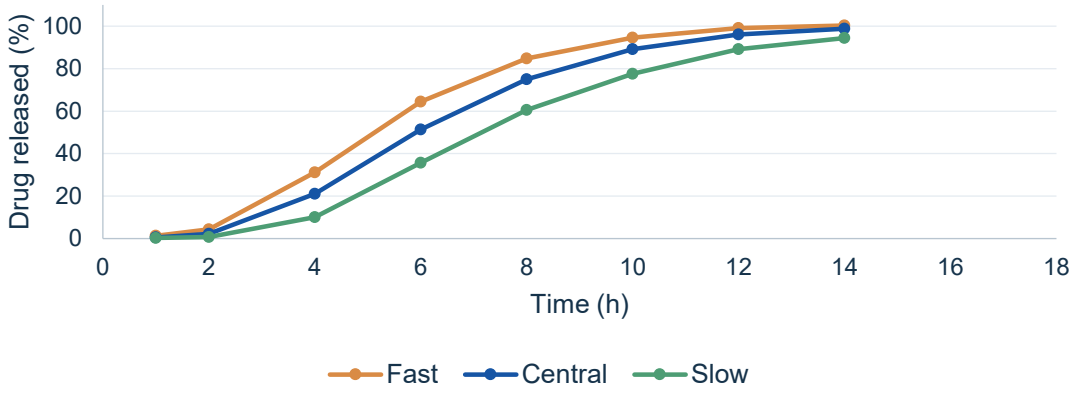
Medium effects require consideration; hydrodynamic sensitivity was limited within the tested conditions.

SANDOZ | lek

Designed release-rate differences are consistently resolved across complementary dissolution conditions

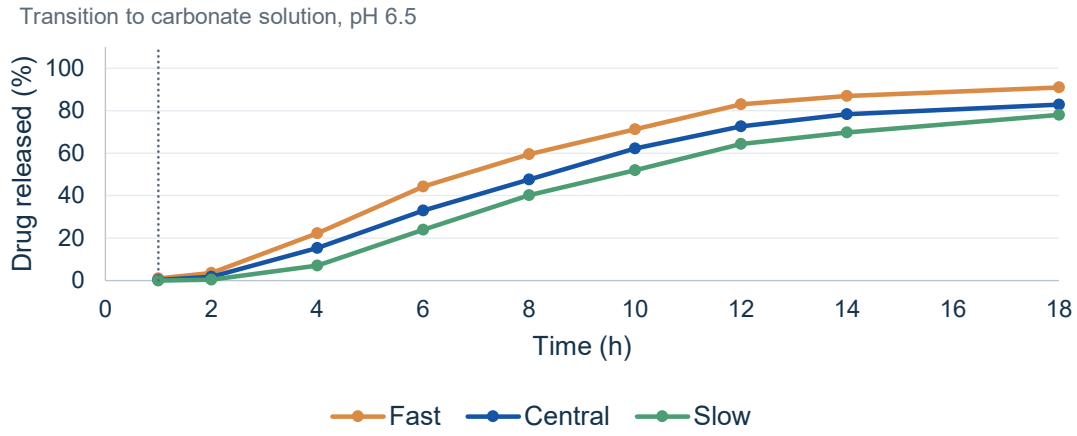
QC method

Water, 900 mL, USP Apparatus 2 with sinker, 50 rpm



Sequential pH-transition method

USP Apparatus 2, 50 rpm, 900 mL; 60 min in 0.01 M HCl with ions followed by carbonate solution pH 6.5



What this establishes

- Deliberate changes in ER-coating amount produced distinct dissolution profiles.
- Both methods retained the Fast > Central > Slow ordering.
- Discrimination was maintained across the two tested dissolution conditions.

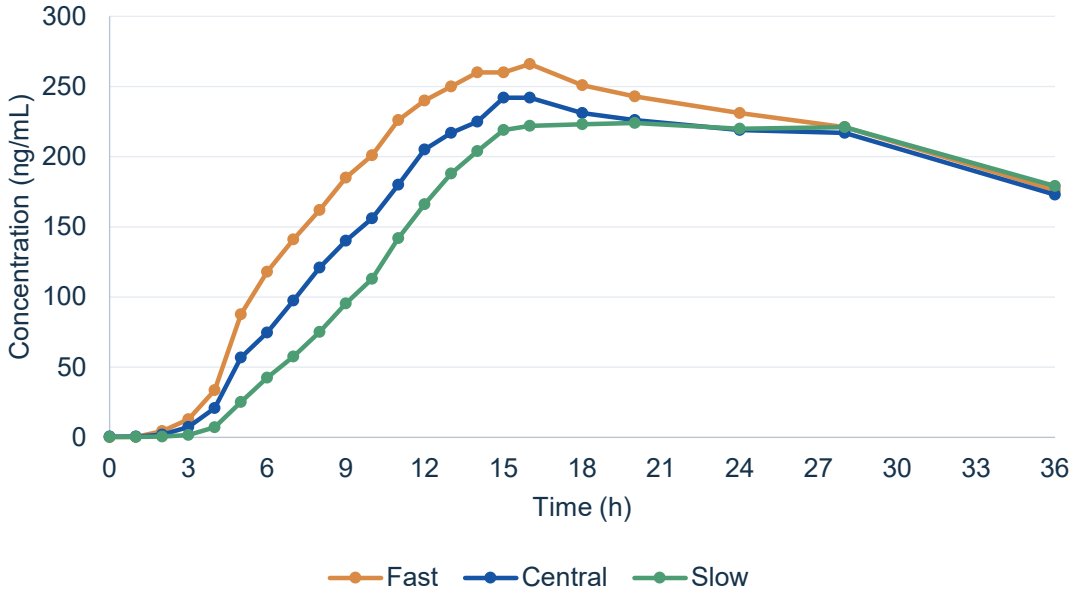
But consistent in vitro discrimination does not, by itself, establish clinical relevance.

SANDOZ | lek

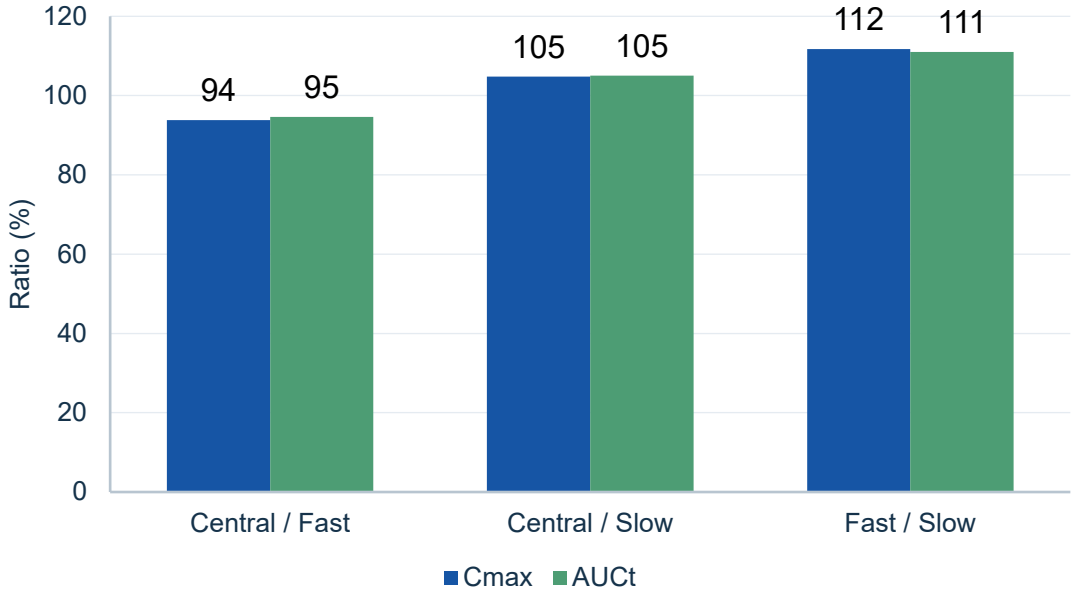
Pilot PK profiles provide the clinical anchor for designed release-rate differences

Fast, Central and Slow variants were evaluated in a fasting pilot crossover study using concentration–time profiles and pairwise Cmax and AUCt comparisons.

Concentration–time profiles



Pairwise Cmax and AUCt point estimates (%)



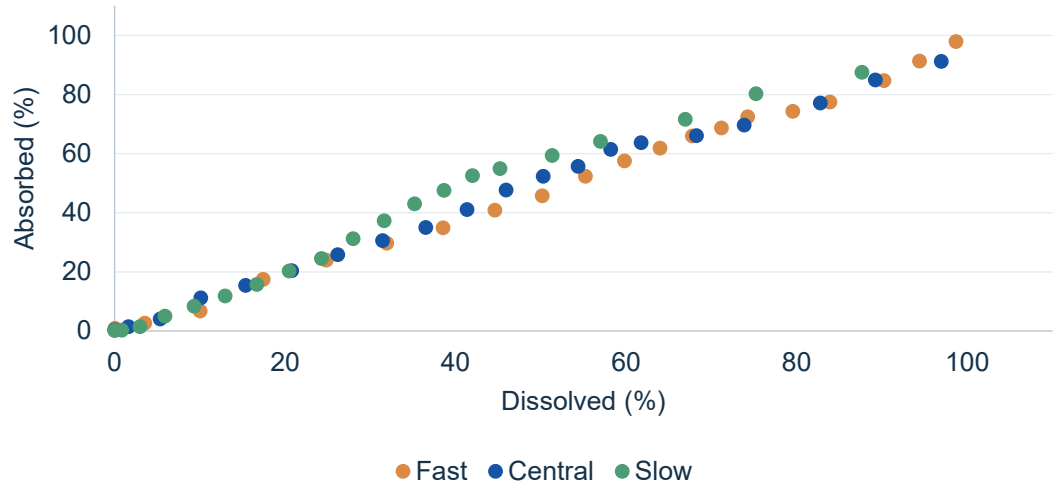
Pilot PK evidence provides a clinical anchor for interpreting dissolution differences.

SANDOZ | lek

Level A IVIVC met internal prediction criteria for three release-rate variants

Water-method dissolution was linked to in vivo absorption using deconvolution and common time scaling.

Time-scaled correlation



Absorbed (%) = 0.9728 × dissolved (%) + 1.1493

$R^2 = 0.98$

Internal prediction performance (PE = prediction error)

Variant	Cmax absolute PE (%)	AUC∞ absolute PE (%)
Fast	0.3%	2%
Central	1%	0.1%
Slow	12%	3%
Reported mean absolute PE	**4.5%**	**1.8%**

Acceptance criteria

Mean absolute PE ≤10%
Individual-formulation absolute PE ≤15%

Water dissolution, Weibull fitting, Wagner–Nelson deconvolution and common Levy time scaling

Dissolution provides a quantitative link to systemic exposure within the evaluated formulation range.

SANDOZ | lek

The conclusion comes from the totality of evidence

No single result carries the strategy. Confidence comes from mutually reinforcing evidence matched to the intended decision.

Product & process understanding	Release-controlling coating functions and controlled manufacturing attributes
Purposeful formulation variants	A designed range of fast, central, and slow performance
Complementary in vitro evidence	QC discrimination, medium sensitivity, limited hydrodynamic sensitivity under tested conditions, and complementary dissolution methods.
Clinical evidence	PBE, pivotal fast, fed, sprinkle BE
Predictive linkage	Level A IVIVC meeting internal prediction criteria within the evaluated formulation range

Stronger basis for a clinically anchored dissolution strategy

- Specification justification
- Risk-based change assessment
- Evaluation of operating flexibility
- Lifecycle decision-making

The endpoint is not a lower label. It is a stronger decision framework.

SANDOZ | lek

From product-specific evidence to risk-based regulatory decisions

How should this evidence inform the next decision?

Specifications — Use the dissolution–exposure relationship to inform specification justification.

Change assessment — Assess changes against the understood release mechanism and the scope of the supporting evidence.

Regulatory flexibility — Use the integrated evidence to support risk-based decisions where justified.

OPEN QUESTION

When is the totality of evidence sufficient for greater regulatory flexibility?

What evidence, and what limits of applicability, should underpin clinically anchored specifications, risk-based change assessment and reduced reliance on additional in vivo studies?

Beyond the default label: confidence should be linked to the decision and bounded by the evidence.

SANDOZ | lek

Sandoz Export Business

Caring for patients Worldwide



SANDOZ