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Challenges In Dissolution Testing Of Pro-Drugs

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Presentation

1. **Understanding Of Pro-Drugs**
   - Definition
   - Bio-transformation
   - Advantages
   - Trends For Pro-Drugs
   - Regulatory Classifications
   - Multiple subtypes
2. **Dissolution Method Development Of Pro-Drugs**
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   - Losartan
3. **Proposed Multi-tiered Logic Approach For Quick Dissolution Method Development For Pro-Drugs**
4. **Influence Of Genetic Variations**

What Are Pro-Drugs?

Definition:

A **pro-drug*** is a medication that is biologically inactive, or at least significantly less active, but once administered into the body is converted to a biologically active drug.

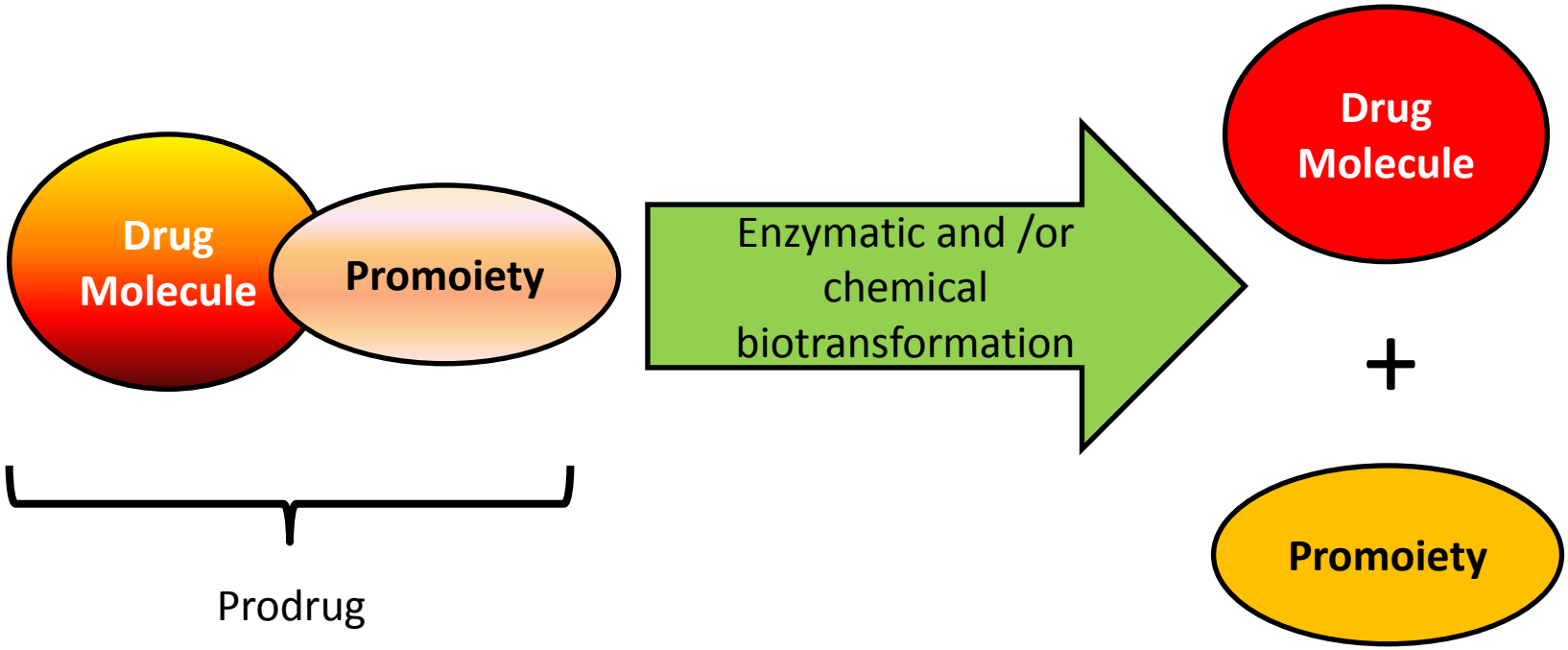
Famous examples of pro-drugs:

- in 1867, Cahn and Hepp developed acetanilide, a pro-drug, which is hydroxylated to biologically active acetaminophen
- In 1897, Felix Hoffman synthesized aspirin (acetylsalicylic acid)
- Heroin is a pro-drug for morphine

*A Albert. Chemical aspects of selective toxicity. Nature 182:421-422, 1958.

Bio-transformation Of Pro-drugs

- Usually via an enzymatic or chemical reaction
- Can be intracellular or extracellular
- Salts of drug molecules are not pro-drugs



Advantages Of Pro-Drugs

1. To improve the:

   Absorption

   Distribution

   Metabolism

   Excretion

   effects of a drug especially when a drug itself is poorly absorbed from the gastrointestinal tract[1] or is to be delivered to a particular site within the body[2]
2. To reduce adverse or unintended effects of a drug.[3]
3. To improve chemical stability of the drug[4]
4. As part of life-cycle management of a drug

1. A Minireview: Usefulness of Transporter-Targeted Prodrugs in Enhancing Membrane Permeability. Murakami T. J Pharm Sci. 2016 Sep;105(9):2515-2526
2. Prodrug Approaches for CNS Delivery Rautio, J.,Laine, K.,Gynther, M., Savolainen, J., AAPS J. 2008 Mar; 10(1): 92–102
3. **Analgesic Prodrugs for Combating their Side-Effects: Rational Approach.** Ruchita[1], Sucheta, Nanda S, Pathak D , Curr Drug Deliv 2017;14(1):16-26
4. **Metronidazole prodrugs: synthesis, physicochemical properties, stability, and ex vivo release studies.** Mura C, Valenti D, Floris C, Sanna R, De Luca MA, Fadda AM, Loy G. Eur J Med Chem. 2011 Sep;46(9):4142-50. doi: 10.1016/j.ejmech.2011.06.016. Epub 2011 Jul 2.

Trends For Pro-drugs

Today, estimated that approximately 10% of all marketed drugs worldwide are pro-drugs. [1,2]

(2010) Dabigatran Etexilate

(2011) Gabapentin Enacarbil

(2013) Sofosbuvir

(2014) Tedizolid phosphate

(2015) Isavuconazonium; Aripiprazole Lauroxil; Selexipag

(2017) Latanoprostene Bunod

1. J Rautio, NA Meanwell, L Di, MJ Hageman. The expanding role of prodrugs in contemporary drug design and development. Nature Reviews Drug Discovery: 2018 April 27
2. J Rautio, J Kärkkäinen, KB Sloan. Prodrugs – Recent approvals and a glimpse of the pipeline. European Journal of Pharmaceutical Sciences 109 : 146-161, 2017.

Regulatory Classifications Of Pro-Drugs*

Class	Conversion Site	Subtype	Tissue Location Of Conversion
I	Intracellular	IA	Therapeutic target tissues or cells
		IB	Metabolic tissues eg liver, lung
II	Extracellular	IIA	GI fluid
		IIB	Systemic circulation
		IIC	Therapeutic target tissue/cells

*KM Wu. A new classification of prodrugs: Regulatory perspectives. Pharmaceuticals 2: 77-81, 2009.

Pro-Drugs Of Multiple Subtypes

Pro-Drugs bioconversion can be:

1) In **parallel** or
2) In **sequential** steps

If in **parallel** (eg in target cells and in systemic tissues), then, the Pro-Drug is expressed as Type IA**/**IB where "**/**" is applied.

If in **sequential** steps (eg in gastrointestinal fluid, then in target cells), then, the Pro-Drug is expressed as Type IIA**-**IA where "**-**" is applied.

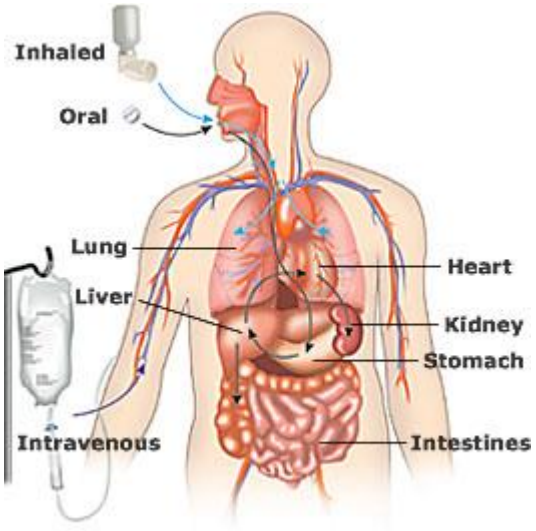
So Is Dissolution Even Relevant For Pro-Drugs?

Seeing a child, predict his/her adulthood behaviour

Selection Of The Correct Dissolution Conditions

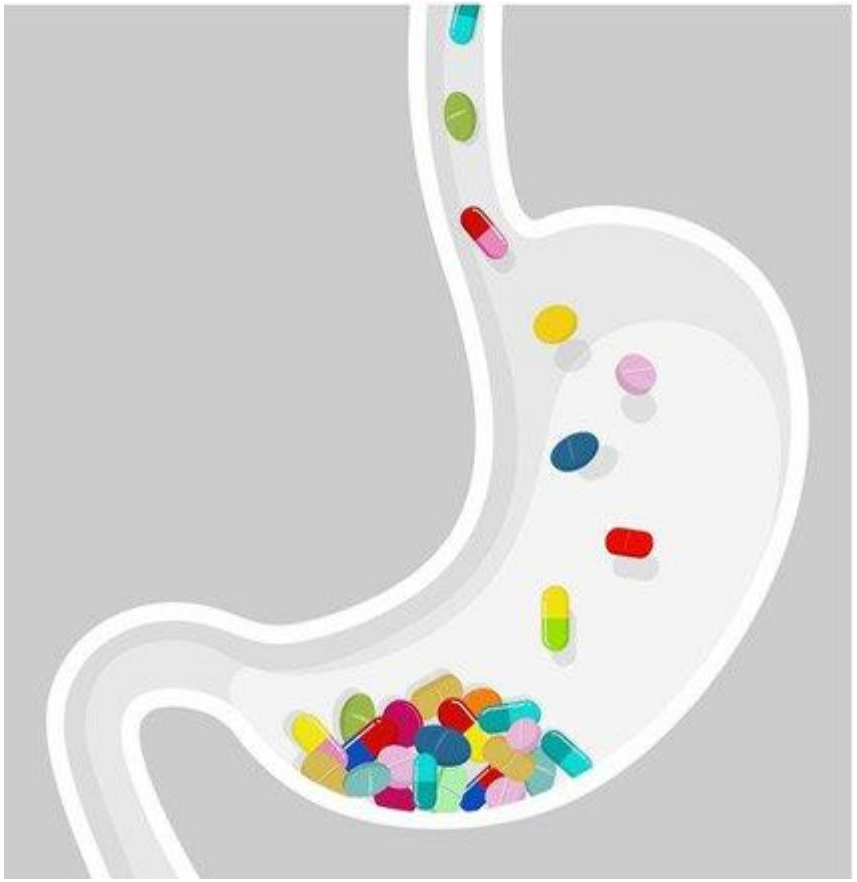
Basis of selection depends on:

- mechanisms of bioconversion (chemical or enzymatic), simple or mixed, parallel or sequential
- preferred location of bio-conversion and
- the residual bioactivity of the unconverted pro-drug (as some pro-drugs are still bioactive even if there is significantly less than the active drug)

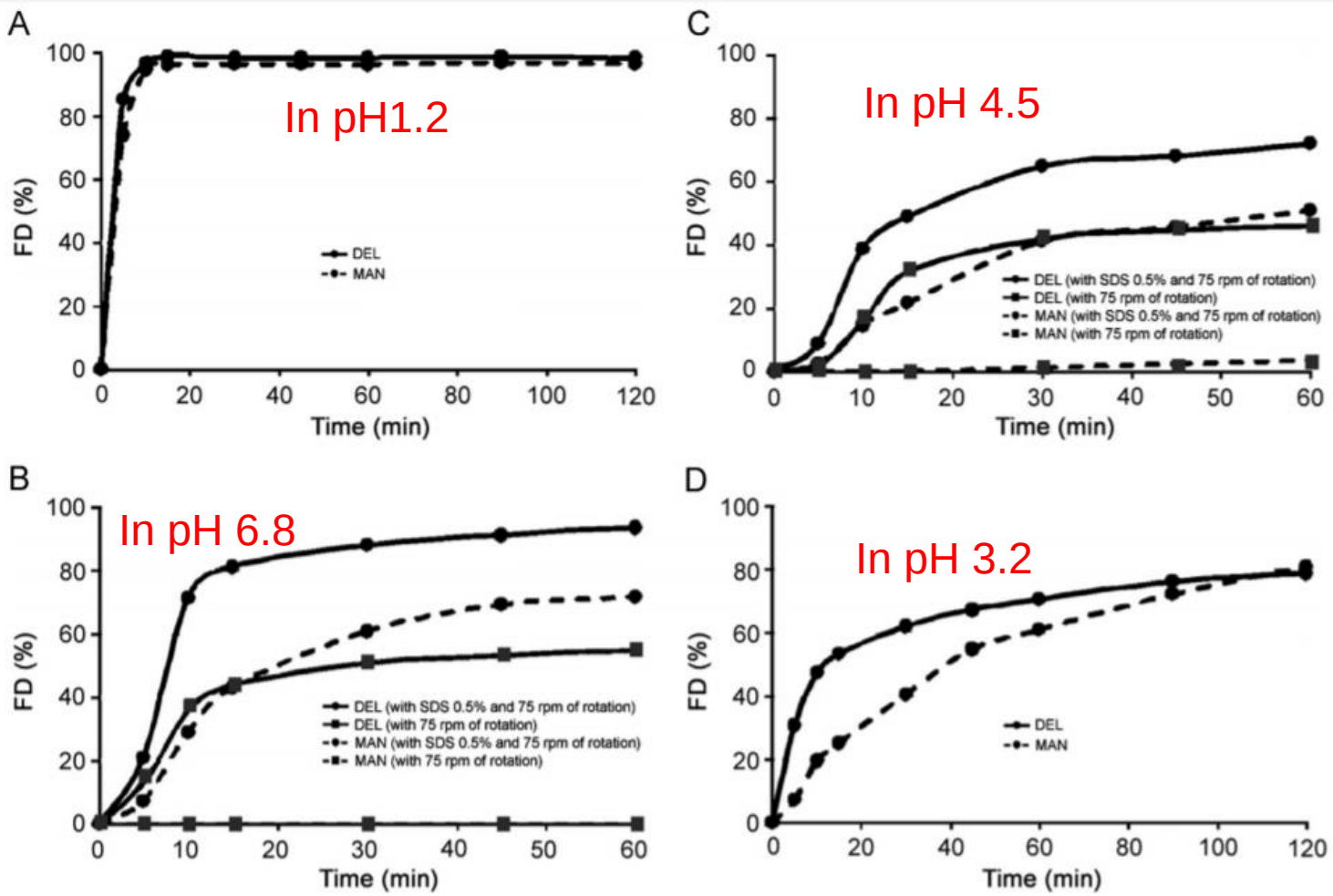


Selection Of The Correct Dissolution Conditions

Understanding of Bio-Conversion	Pro-Drug Characteristics
Mechanism	Chemical
Single or Multiple	Single
Preferred Location	Stomach
Rate	Very fast
Residual Activity Of Unconverted Pro-Drug	Nil



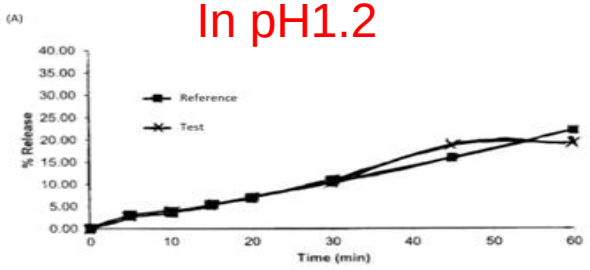
Successful Dissolution Prediction Of Delapril In Delapril + Manidipine Tablets*



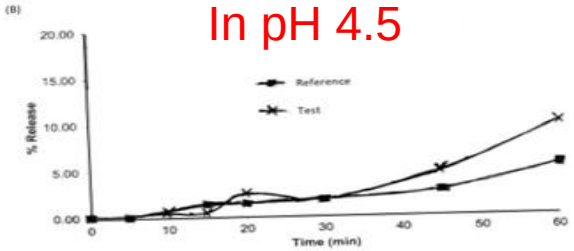
*V Todeschini, MS Sangoi, GK Goelzer, JC Machado, CS Paim, BV Araujo, NM Volpato. Dissolution method for delapril and manidipine combination tablets based on an absorption profile of manidipine. Journal of Pharmaceutical Analysis 6:49-55, 2016.

Dissolution Of Losartan In Losartan + HCT Tablets

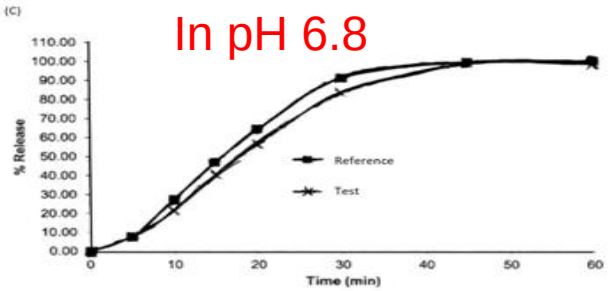
In pH1.2



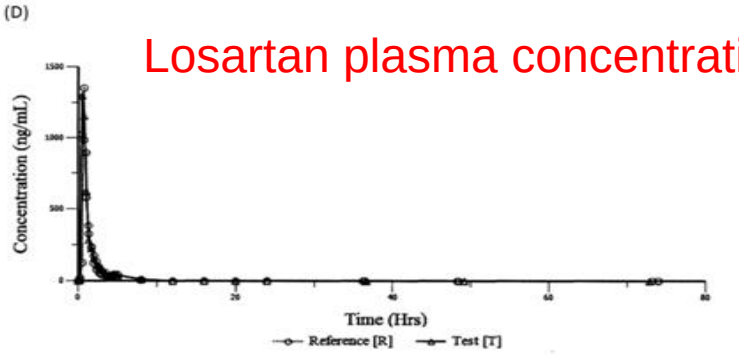
In pH 4.5



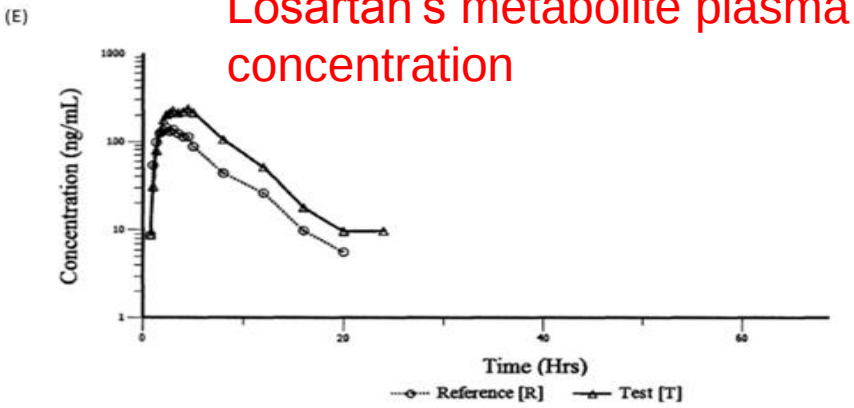
In pH 6.8



Losartan plasma concentration



Losartan's metabolite plasma concentration



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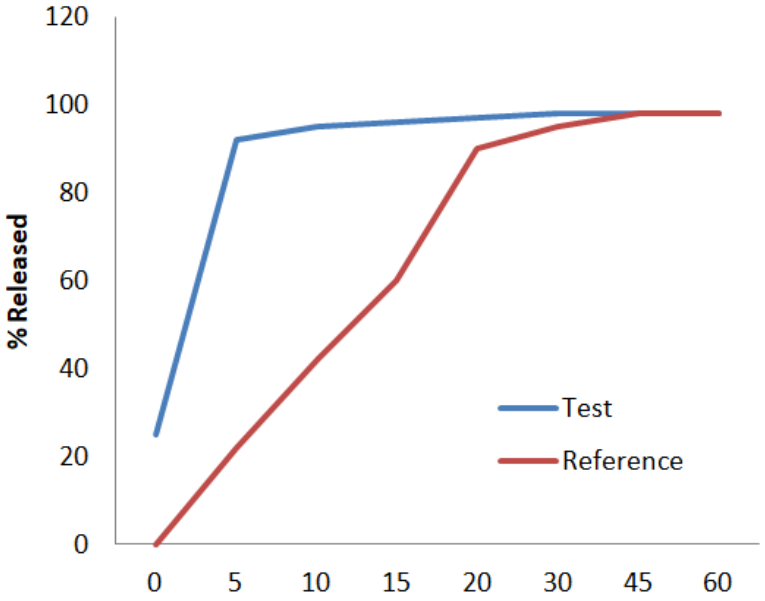
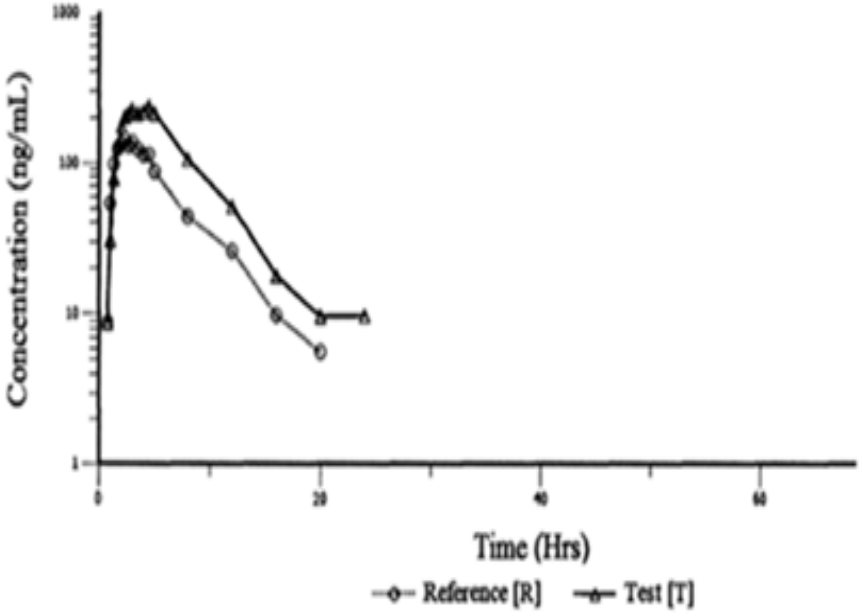
Successful Dissolution Prediction Of Losartan in Losartan + HCT

In pH 3.0 FaSSGF



Losartan's metabolite plasma concentration



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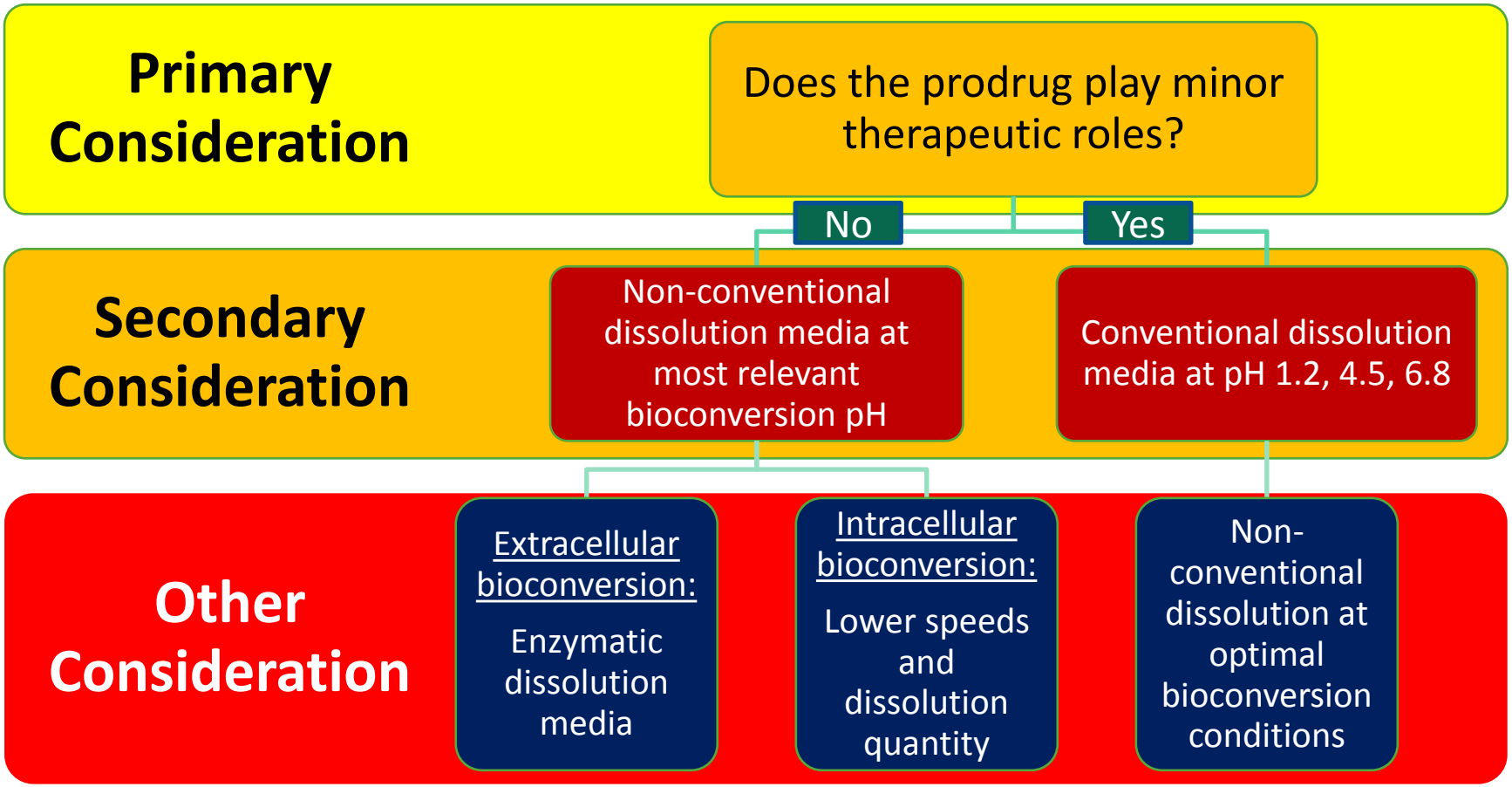
Proposed Multi-tiered Logic Approach For Quick Dissolution Method Development For Pro-Drugs



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Influence Of Genetic Variation On Pro-Drugs*

Table 2. Incidence of Cytochrome P450 Metabolizer Phenotypes Among Ethnic Groups

Enzyme	Metabolizer phenotype	Population frequency (%) Asians	Blacks	Whites
CYP2C9	Poor	0.4[3]	0.0[4]	1.0[4]
	Intermediate	3.5[4]	13[4]	33[4]
	Ultrarapid	—	—	—
CYP2C19	Poor	18 to 23[3,5]	1.2 to 5.3[5,6]	2.0 to 5.0[3,5]
	Intermediate	30[7]	29[7,8]	18[7]
	Ultrarapid	—	—	—
CYP2D6	Poor	1.0 to 4.8[3,5,8]	1.9 to 7.3[5,6,8]	7.0 to 10[3,8]
	Intermediate	51[8]	30[9]	1.0 to 2.0[8]
	Ultrarapid	0.9 to 21[8]	4.9[8]	1.0 to 5.0[8]

NOTE: *Poor metabolizers have markedly reduced or absent enzyme activity; intermediate metabolizers have reduced enzyme activity; and ultrarapid metabolizers have high enzyme activity.*

CYP = cytochrome P450.

Information from references 3 through 9.

*DJ Belle, H Singh. Genetic Factors in Drug Metabolism. American Family Physician. 77 (11): 1553-1560, 2008

Need For Genetic Profiling When Pro-drugs Are Tested?

Table 3. Clinical Consequence of Metabolizer Phenotypes on Drug Response

Drug type	*Metabolizer phenotype*	*Effect on drug metabolism*	*Potential consequence*
Prodrug, needs metabolism to work (e.g., codeine metabolized to morphine)	Poor to intermediate	Slow	Poor drug efficacy, patient at risk of therapeutic failure
			Accumulation of prodrug, patient at increased risk of drug-induced side effects
	Ultrarapid	Fast	Good drug efficacy, rapid effect

NOTE: *Poor metabolizers have markedly reduced or absent enzyme activity; intermediate metabolizers have reduced enzyme activity; and ultrarapid metabolizers have high enzyme activity.*

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Conclusion

Dissolution testing is still a useful predictor of performance in pro-drugs

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