Bioavailability/Bioequivalence Studies in Evaluation of New Levothyroxine Products

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Introduction

- Introduced in the 1950s

  (more pure, synthetic form of Thyroid, USP)

- Prior to August, 2000, levothyroxine sodium was an unapproved marketed drug

- In 1997 at least 37 manufacturers or re-packagers of levothyroxine sodium tablets

Federal Register Notice (62 FR 43535)

- In an effort to standardize levothyroxine sodium tablets, and to reduce the instances of sub- and super-potency problems, on August 14, 1997, the FDA declared levothyroxine sodium tablets a “new drug”

- Sponsors wishing to continue to market their product needed to submit an NDA or file a citizen’s petition describing why an NDA was not necessary

FDA Guidance for Industry

Levothyroxine Sodium Tablets - *In Vivo* Pharmacokinetic and Bioavailability Studies and *In Vitro* Dissolution Testing -- Feb. 2001

- Introduction and Background
- *In vivo* pharmacokinetic and bioavailability studies
  - Inclusion criteria
  - Single-dose (relative) bioavailability (to solution)
  - Dosage-form proportionality
- *In vitro* dissolution testing
- Formulation
- Biowaiver
- Assay validation

Questions Were:

- Is the bioavailability of the product known? (no)
- Is the bioavailability optimal? (unknown)
- Do levothyroxine tablets have the proper, labeled amount of drug? (no)
- Do the tablets contain a consistent amount of drug? (no)
- Does the drug dissolve rapidly and completely? (unknown)
- Is the drug stable over time? (no)
- Will subsequent batches perform the same as a batch tested for bioavailability? (unknown)

Product Stability

- Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients
- Between 1990 and 1997:
  - 10 recalls, 150 lots, and 100 million tablets
    - content uniformity, sub-potency, and stability failures
- Many products were manufactured using an overage

PRODUCT	% of LABELED CLAIM
Flint (Synthroid™)	106% – 109%
USV	101%
Geneva – Zenith	93% – 108%
Rugby	107%

Fish et al. (1987)

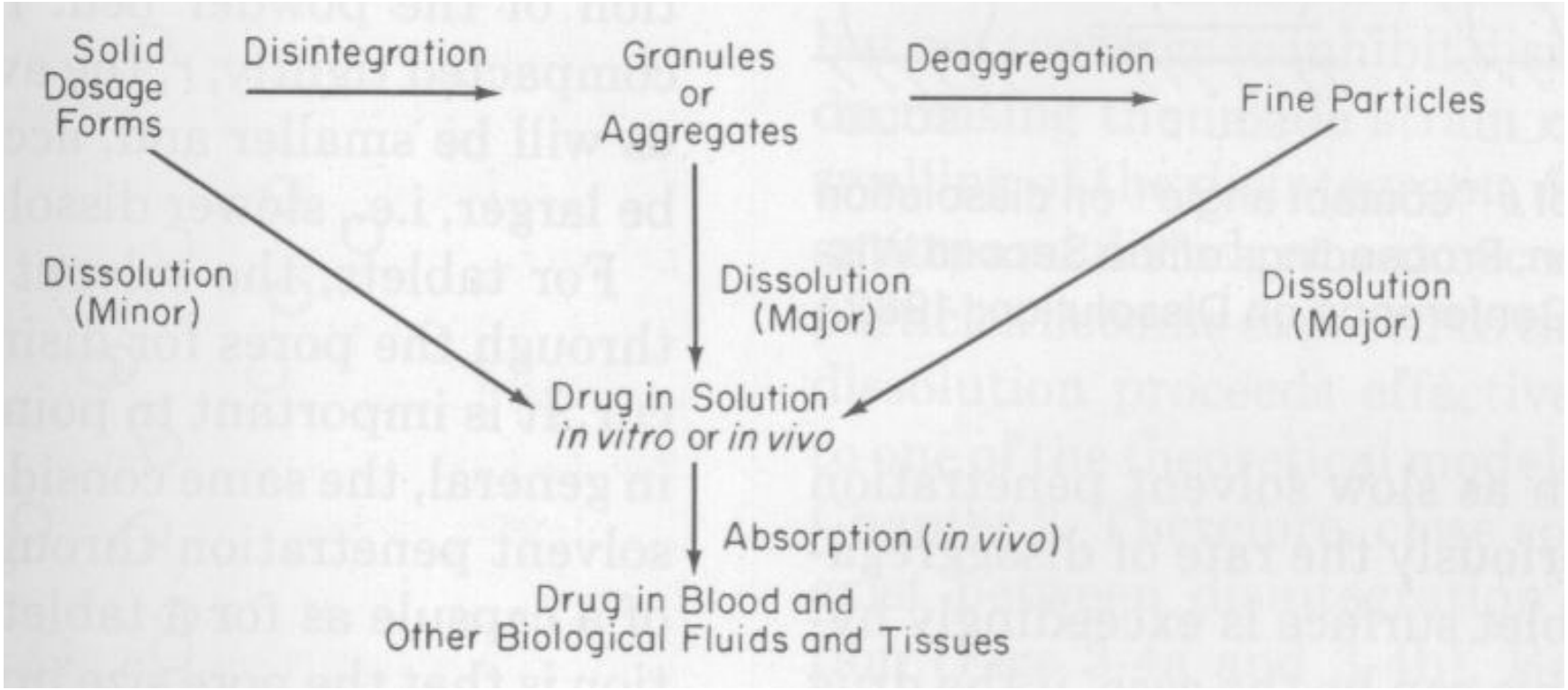
Levothyroxine Label

- Absorption 40-80%
- Decreased by soybean infant formula, fiber, walnuts
- Many drugs and foods affect absorption
- Take on empty stomach ½-1 hour before breakfast

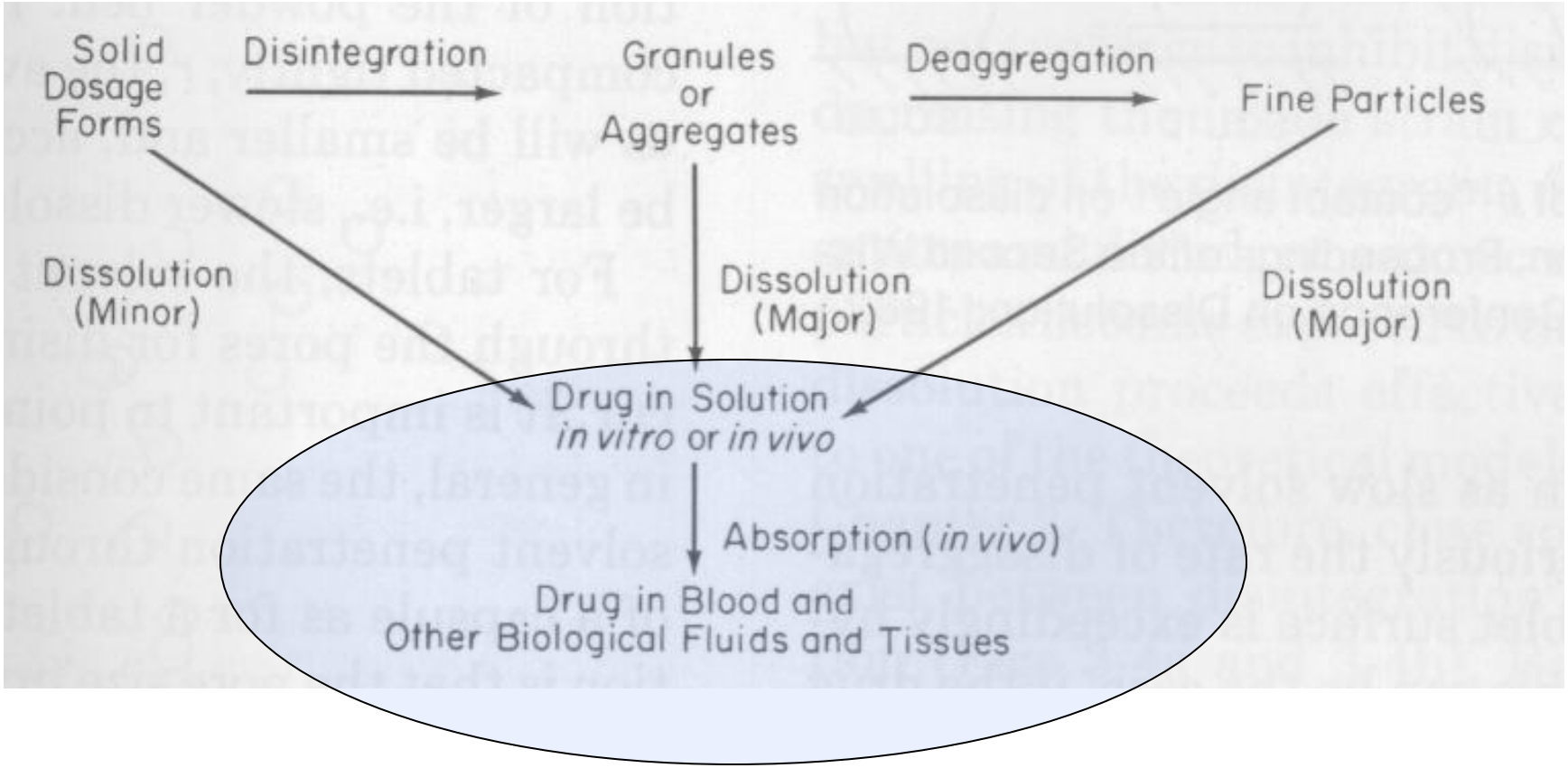
Drug Absorption

- GI transit to site of absorption
- Dissolution
- Absorption

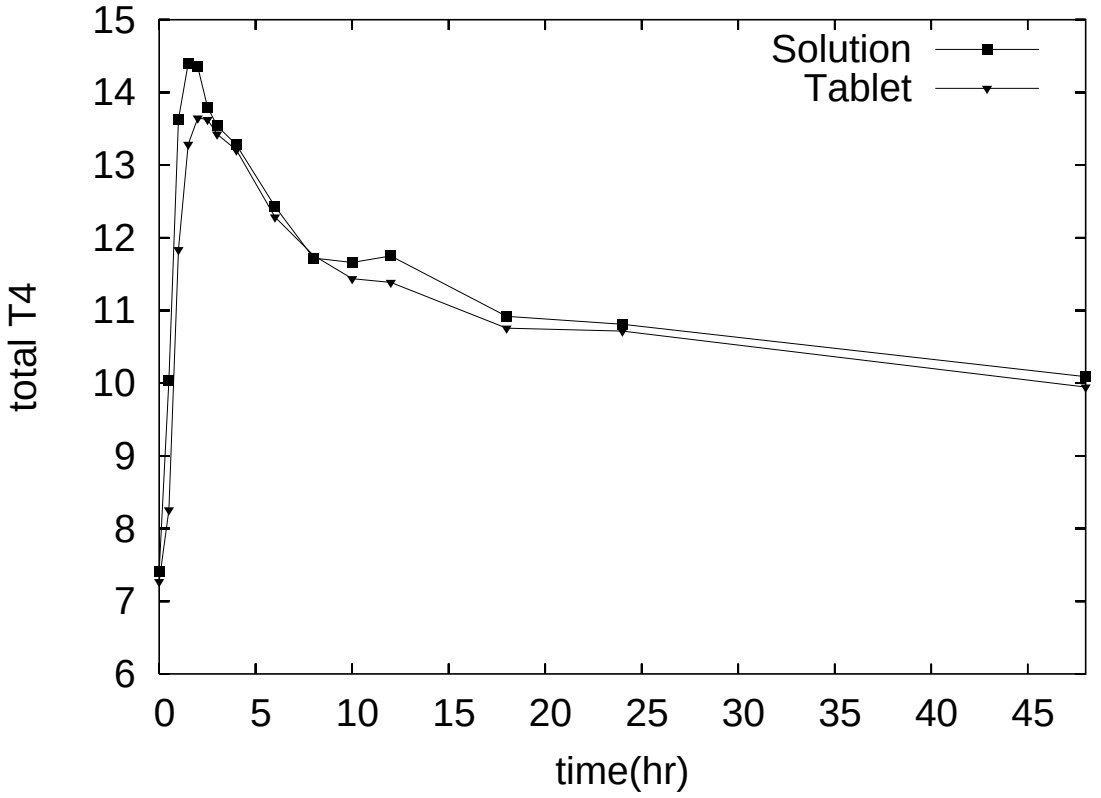
From Tablet to Drug Absorption



From Tablet to Drug Absorption



Typical Results for Solution Study

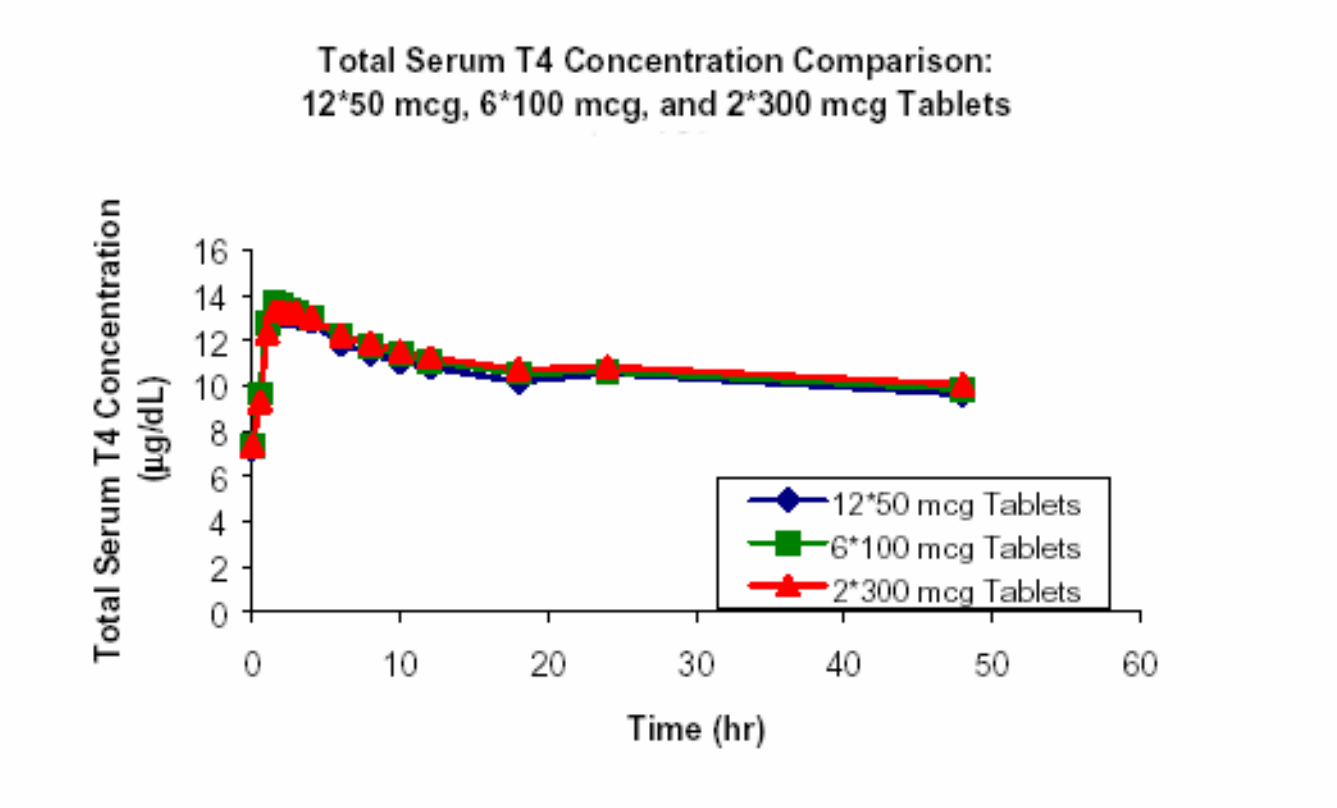


Typical Results for Solution Study

Table 8. Summary of the Pharmacokinetic Parameters of Serum T4 and T3 for Treatment A and B

	T4			T3			
	Treatment A	Treatment B			Treatment A	Treatment B	
PK Parameters	Arithmetic Mean ± SD	Arithmetic Mean ± SD	%Mean Ratio* (90% CI)	PK parameter	Arithmetic Mean ± SD	Arithmetic Mean ± SD	% Mean Ratio* (90% CI)
Cmax (μg/dL)	14.48 ± 1.93	15.09 ± 2.10	----	Cmax (ng/mL)	1.165±0.156	1.140 ± 0.119	----
Tmax (hr)	2.17 ± 0.810	1.62 ± 0.502	----	Tmax (hr)	14.6 ± 15.2	16.3 ± 17.0	----
AUC(0-t) (μg·hr/dL)	524.3 ± 59.07	529.3 ± 62.83	----	AUC(0-t) (ng·hr/mL)	51.25±6.163	50.07 ± 5.311	----
ln(Cmax)	2.663 ± 0.1434	2.705 ± 0.1339	94.5 (91.1–98.1)	ln(Cmax)	0.1444± 0.1289	0.1255±0.1034	100.0 (96.8-103.4)
ln[AUC(0-t)]	6.256 ± 0.1167	6.265 ± 0.1169	98.0 (95.6-100.5)	ln[AUC(0-t)]	3.930± 0.1209	3.908± 0.1059	100.7 (97.7-103.8)

Typical Results for Dosage Strength Comparison Study



Typical Results for Dosage Strength Comparison Study

Table 9. Summary of the Pharmacokinetic Parameters of Serum T4 for Treatment A, B and C

	Arithmetic Mean ± SD			% Mean Ratio* (90% CI)		
Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C	A vs. B	B vs. C	A vs. C
Cmax(µg/dL)	13.70 ± 1.82	14.13 ± 1.48	14.15 ± 1.50	---	---	---
Tmax (hr)	2.37 ± 1.04	1.98 ± 0.827	2.40 ± 1.09	---	---	---
AUC(0-t)(µg·hr/dL)	509.0 ± 58.36	528.3 ± 72.41	528.7 ± 57.13	---	---	---
ln(Cmax)	2.609 ± 0.1378	2.643 ± 0.1095	2.644 ± 0.1085	96.8 (93.6 – 100.1)	100.0 (96.7 – 103.4)	96.8 (93.6 – 100.1)
ln[AUC(0-t)]	6.226 ± 0.1200	6.261 ± 0.1379	6.265 ± 0.1089	96.7 (93.4 – 100.0)	99.7 (96.4 – 103.1)	96.4 (93.1 – 99.7)

NDAs

- Between June 1999 and July 2001, several sponsors submitted NDAs
- The first product was approved in August, 2000
- There are currently seven approved levothyroxine sodium tablet NDAs

Formulation

- Must target 100% of label claim
- No unaccountable or “stability” overages
- Currently approved products have precise CMC requirements, dissolve rapidly and are stable. Therefore, minimal bioavailability concerns. (behave like a solution)

Answers Now Are:

- Is the bioavailability of the product known? **yes**
- Is the bioavailability optimal? **yes**
- Do levothyroxine tablets have the proper, labeled amount of drug? **yes**
- Do the tablets contain a consistent amount of drug? **yes**
- Does the drug dissolve rapidly and completely? **yes**
- Is the drug stable over time? **yes**
- Will subsequent batches perform the same as a batch tested for bioavailability? **yes**

Conclusion

- The process used by FDA for the 7 approved NDAs for levothyroxine products has addressed concerns related to the quality of these products.
- These products can be used with confidence knowing that bioavailability and product quality are consistent and high.
- Any products which fail specifications will be removed from the market.