REGULATORY PERSPECTIVE

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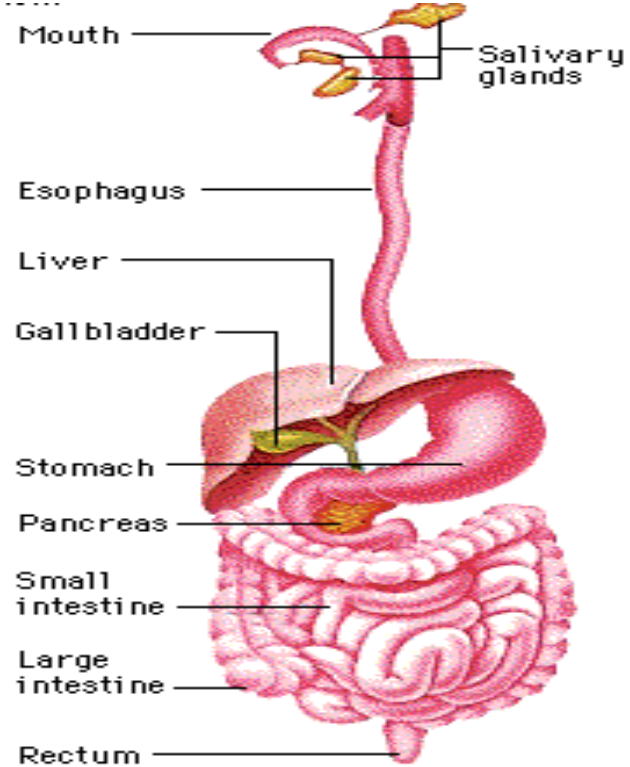
Contents

Does In-vitro Dissolution meeting In-Vivo requirement?



- **Disintegration**
- Solids transfer
- **Dissolution**
- **Changing pH**
- **Food and drink**
- Absorption
- Clearance

10-10-2013 FDA Update:
Bupropion Hydrochloride
Extended-Release 300 mg
Bioequivalence issue – Watson recalled (product equivalence code changed to AB to BX)
Welbutrin XL 300 mg (Innovator product was RLD)

Ref.Website: http://www.google.com/images - Digestion System

Pharmaceutical Dissolution and its importance Today

Application Type	Format
NDA	eCTD
SNDA	eCTD
BLA	eCTD/eBLA
ANDA	eCTD
IND	eCTD/eIND

15000 Generics have been approved by FDA till date in US alone
Total Market Cap is more than 150 Billion USD

NDA- New Drug Application; SNDA- Supplement New Drug Application;BLA-Biologic License Application; ANDA-Abbreviated New Drug Application ; IND-Investigational New Drug Application

Dissolution Test in Approving the Generic Drugs

Requirements:

- Life Cycle of the Generic product (SUPAC)
- Robust Rugged, highly discriminating dissolution Methods (OGD,DBE)
- Minimum 12 units to be tested (both innovator and Test Product)
- Minimum 3 to 4 times sampling with equal spacing other than Zero Time for Immediate Release Products more for Extended Release Tablets

Merits of Dissolution Studies – Approval Process(CMC)

1. *In vitro* dissolution testing is an important tool for development and **approval of generic dosage forms.**
2. Routinely used for stability and **quality control purposes** for both oral and non-oral dosage forms.
3. Reduces the **Regulatory Burden for approval by reducing the clinical without sacrificing Quality**

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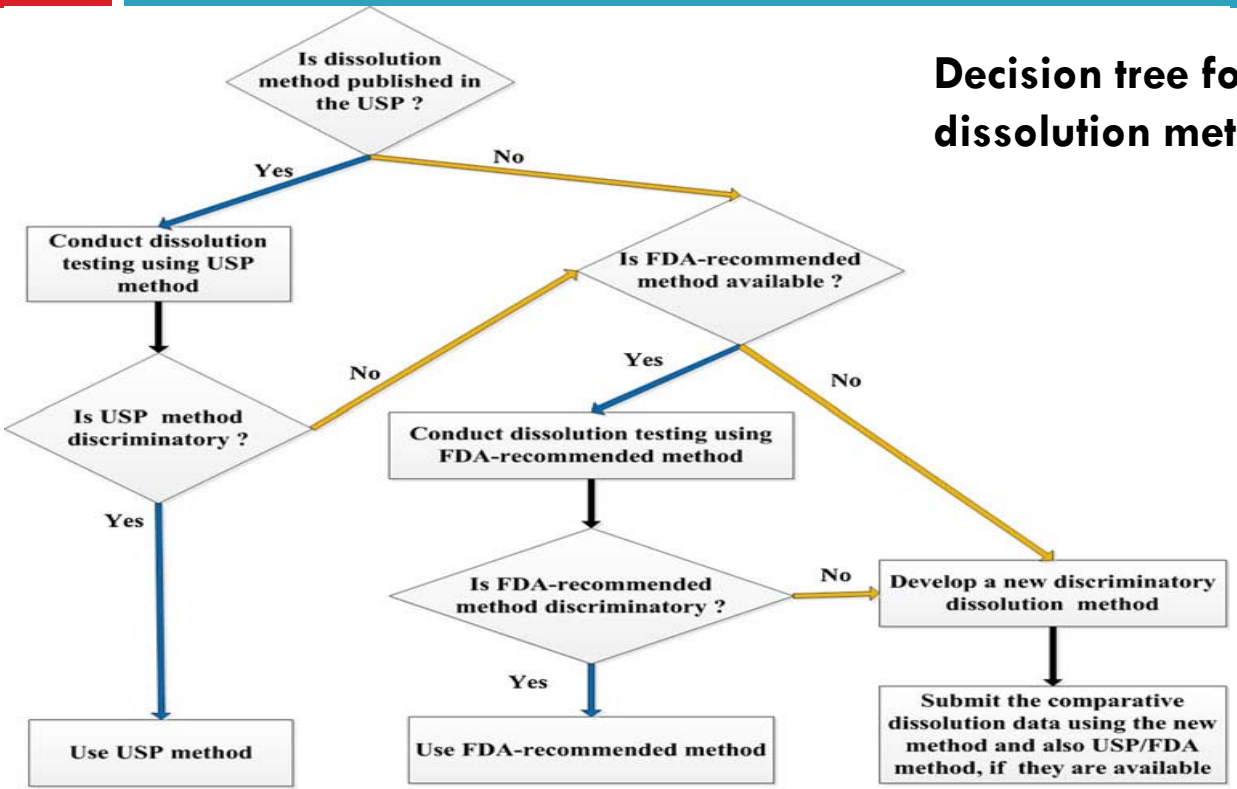
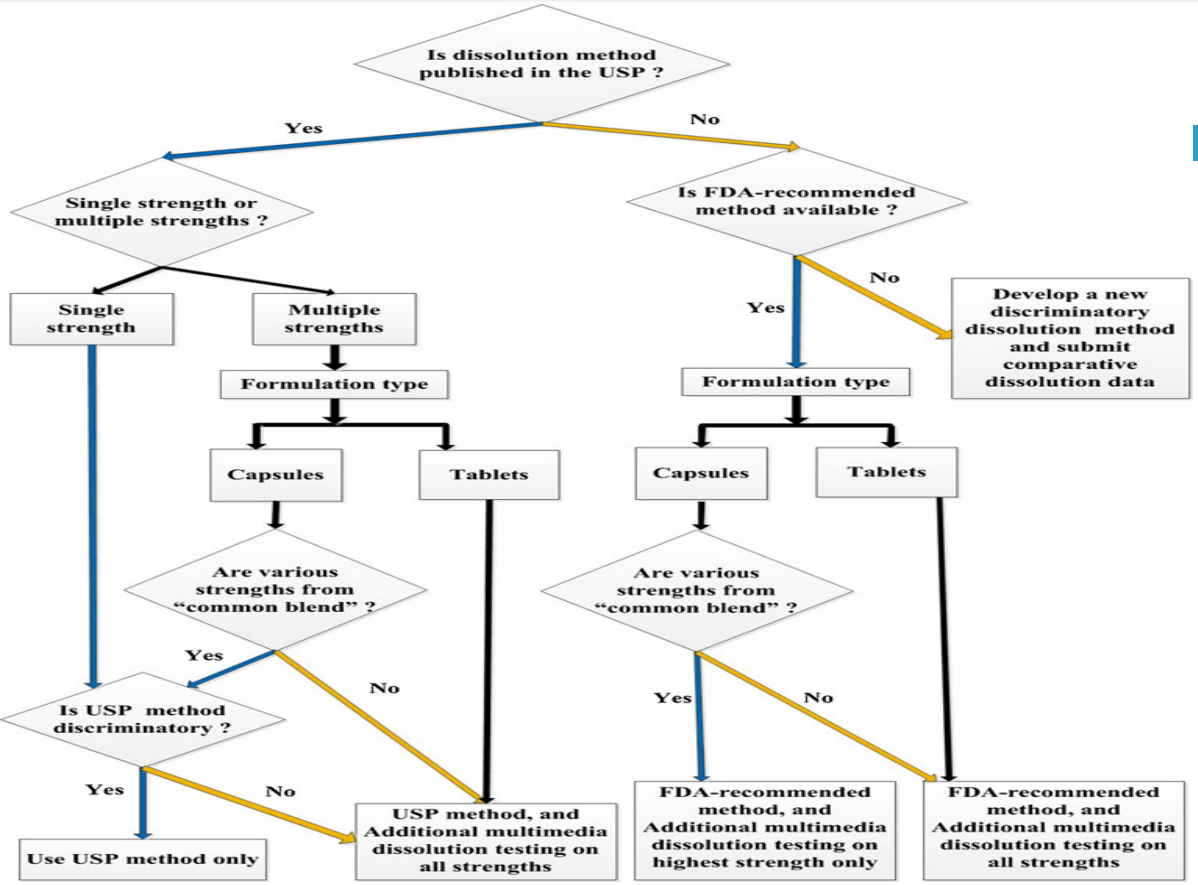
Dissolution Method for Generic Product



Decision tree for ANDA sponsors to select a dissolution method for their generic product

Decision Tree for Extended Release Dosage Form



Decision-tree for ANDA sponsors for submitting dissolution testing data for an extended-release solid oral generic drug product. {"Common blend": A batch of final blend that can be packed in different amounts providing various strengths of the capsule product. Multimedia: lower pH, e.g. 1.2; medium pH, e.g. 4.5; higher pH, e.g. 6.8 and water}

Dissolution Testing and BCS Based Bio-waivers

Bio-waiver for Rapidly Soluble Drugs

21 CFR part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications.

21 CFR part 320:22 address the waivers

BCS Classification

Class 1 – **High Solubility, High Permeability**

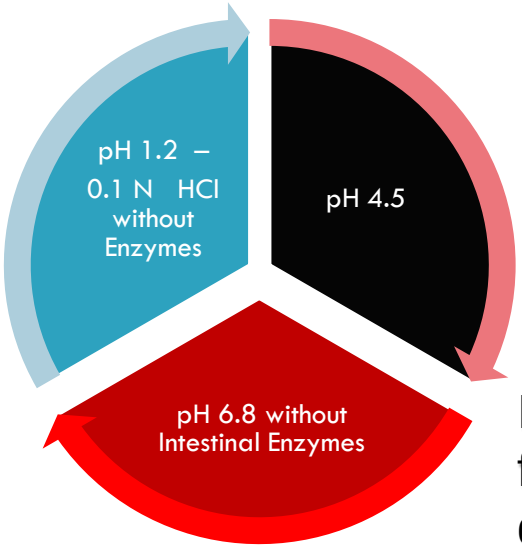
Class 2 – **Low Solubility, High Permeability**

Class 3 – **High Solubility, Low Permeability**

Class 4 - **Low Solubility – Low Permeability**

Ref.:Food and Drug Administration. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a bio-pharmaceutics classification system. Rockville, MD: US Department of Health and Human Services, FDA, Centre for Drug Evaluation and Research; August 2000.

Dissolution – Bio-waiver BCS Class I



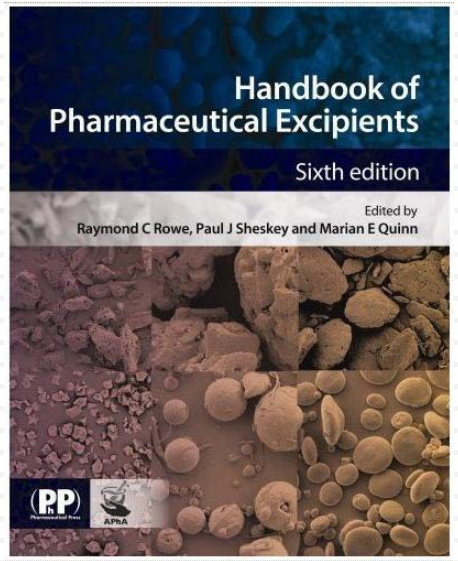
85% of the Drug Release in **30 minutes** using **Type I @ 100 RPM** Or 85% of the Drug Release in 60 minutes using **Type II @ 50RPM**

If BE to the reference listed drug has been established for the one strength (generally the highest) of a generic drug **product line then**, as per FDA's General Guidance on Bioavailability and Bioequivalence for Orally Administered Drug Products (BA/BE Guidance)

Bio-waiver for Generic BCS Class I

- Dissolution can also be used to support applicant requests for bio-waivers for various ***strengths of a modified-release (Modified Release) drug product line***.
- In this case, the DBE (Dept. Of Bio Equivalence) may decide that it is unnecessary to conduct in vivo studies on one or more strengths based on acceptable dissolution performance, proportional similarity among strengths, and an acceptable in vivo study on one (***generally the highest***) strength.

SUPAC


Handbook of
Pharmaceutical Excipients
Sixth edition
Edited by
Raymond C Rowe, Paul J Sheskey and Marian E Quinn
PP
APhA

SUPAC

Change		
Site	Composition	Scale, Process and Equipments

- SUPAC IR (immediate release)
- SUPAC MR (modified release)
- SUPAC IR/MR equipment addendum
- SUPAC IR Q&A
- SS: Non sterile semi-solids + equipment addendum

Components and composition

Levels of change: Likelihood of impact on formulation quality and performance

Level 1: **unlikely** to have detectable impact

Level 2: **could have** significant impact

Level 3: **likely** to have significant impact

Components and composition

Level 1 changes: **Quantitative only** (except IR: colour, flavour, ink; MR: + preservative).

Level 2 changes: Quantitative more than Level 1, plus any change in excipient grade (MR: + change in excipient specifications).

Level 3 changes: Quantitative More than Level 2, plus addition or deletion of an excipient (except for a colour, flavour, ink).

Level 1 changes

Addition or deletion of a colour or flavour, or change in an excipient (or preservative (MR))

Changes less than the following table level 1 column (expressed as percentage of the total formulation)

[Note that total additive effect should not exceed 5% of total target FPP weight]

Composition – Level 3 Changes

- Any change beyond level 2 **OR:**
- Any level 2 change for a BCS class 4 (**low solubility and low permeability**) **or narrow therapeutic drug**
- **Drugs not meeting the level 2 dissolution testing**

For both level 2 and level 3 changes, therapeutic range, solubility and permeability are factors to consider.

SUPAC – L1 /L2 Changes – OSD Example

Additive	Excipient (%)	
Type	L1	L2
Filler	+/-5	+/-10
Disntigrant **Starch**	+/-3	+/-6
others	+/-1	+/-2
Binders	+/-0.5	+/-1

Recommended documentation – level 1/2

Requirements for ***level 1*** include ***Stability testing: one batch on long-term stability data reported in annual report.***
Supportive dissolution data: none
Supportive in-vivo bioequivalence testing: ***none***

Requirements for ***level 2*** include stability testing, dissolution testing and possibly an ***in-vivo*** study (depending on the results of dissolution testing).
IR guideline: the dissolution testing required depends on the **BCS class** of the API.
MR guideline: the dissolution testing depends on the **type of release** of the FPP.

Recommended documentation – level 3

Requirements for level 3 *include stability testing, dissolution testing and an in-vivo study.*

Formulation Changes (Application Vs Reviewer)

Sponsor (Change in formulation in % in lubrication stage)

- Lactose 4.05
- Magnesium stearate 0.49
- Talc 1.94
- Colloidal silicon dioxide (SiO_2) 1.62

Assessors or Reviewer

- Lactose 4.05 – L1 (filler)
- Magnesium stearate 0.49 – L1- (Lubricant)
- Talc 1.94-L2 (Glidant)
- Colloidal silicon dioxide (SiO_2) 1.62 –L2 (Talc)

Composition – Level 1/2 Changes – Formulation Change

Excipient	% Excipient	
Lubricant	*L1*	*L2*
Calcium or Magnesium Sterate	+/- 0.25	+/- 0.5
Glidant	+/- 1	+/- 2
Talc	+/- 0.1	+/- 0.2
Others Film Coat	+/- 1	+/- 2

API was of low solubility and Mag. Sterate will have impact on Dissolution Hence Border Level 2

Summary of SUPAC

SUPAC does:

- discuss relative changes in formulation
- discuss supporting data to support a change
- give an idea of how to consider various changes by looking at the change coupled with the API characteristics

SUPAC does not:

- substitute for critical thinking (e.g. formulation changes for modified release products)

Manufacturing Change

Level 1

- Change in the Validation Range - Mixing Time, Blending Time

- **Recommendation** One Batch on Long Term Stability

Level 2

- Change in Mixing Speed – within Validated Range

- **Recommendation** One Batch on Long Term Stability & Dissolution

Level 3

- Change in Manufacturing Process – Wet to Dry Granulation

- **Recommendation** One Batch on Long
- Term Stability, Dissolution & BE

Drug Dumping due to Alcoholic Beverages

HydroMorphone – MR Dosage Form – Drug Dumping

1. Modified Dosage form – Steady Release of Drug.
2. Sponsor of ANDA must study the effect of Alcohol along with the RLD and submit the data
3. RLD and Sponsor Product (ANDA) to be subjected to dissolution in 0.1N HCl along with - 0%,5%,20% & 40% ethanol (Every 15 min one sampling over a period of 120 min)

Ref : FDA's ACPS Meeting, October 2005 Awareness Topic: Mitigating the Risks of Ethanol Induced Dose Dumping from Oral Sustained/Controlled Release Dosage Forms

DESI Drugs Approval

History of Drug Approval @ USA

- Drug Approval Based on the Safety Only at USA(1938-1964)
- Kafauver Harris Amendment to D & C act at USA
- NAS (National Academy of Science) and NRC (National Research Council) – Responsible for Drug Efficacy Study
- DESI Implementation at USA & DESI Drug List Prepared
- Equivalent Code of AA started

Dissolution Test – Other Oral Products

Other Oral Dosage Forms

- Suspensions can be considered to be similar to disintegrated forms of solid formulations.
- DBE generally recommends the use of USP apparatus 2 (paddle) at 25 or 50 rpm for suspension.
- Liquid Filled Capsule Containing the lipophilic Drug – DBE recommends "Rupture test"& release of the content into the media
- Chewing Gums – *In-vitro drug Dissolution Test – Complex system*

Non Oral Dosage Forms

Non Oral Dosage Forms

- For non-oral dosage forms the test is referred as "drug release" rather than "dissolution"
- It is essential to have the efficacy testing as part of the Dossier development.
- DBE and FDA encourages the Sponsors to develop methods (discriminating)
- Type 4 Flow through is recommended
- Ointments, Creams, Lotions – ANDA –*In-vitro Dissolution Study* will not be a surrogate for *in-vivo (However Franz Cell diffusion study for the SUPAC in semisolid)*