

Disintegration



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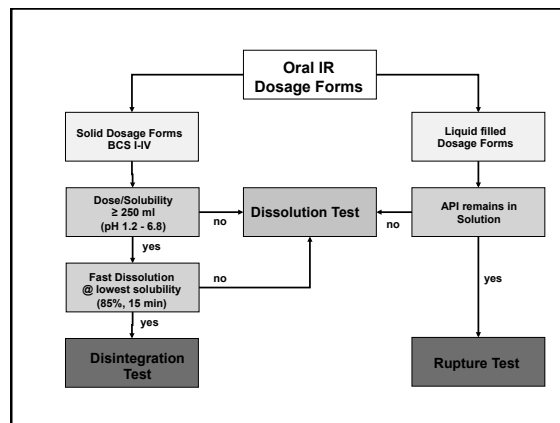
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Historical Perspective
A mini review of scientific and pharmacopeial requirements
for the disintegration test

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USP Performance Test Scheme

Pharmaceuticals	Dietary Supplements
<301> Acid-Neutralizing Capacity	<1216> Tablet Friability
<701> Disintegration	<2040> Disintegration and Dissolution of Nutrition
<711> Dissolution	
<724> Drug release	Supplements
<785> Osmolarity	<2091> Weight Variation
<905> Uniformity of Dosage Forms	<2750> Manufacturing Practices of Dietary Supplements
<1087> Intrinsic Dissolution	
<1088> In vitro and in vivo Evaluation of Dosage Forms	<2090> Weight Variations of Dietary Supplements
<1090> In vivo Bioequivalence Guidance	
<1216> Tablet Friability	

Disintegration in USP 29

Dosage Form	<701>	<701>	<2040>	<2040>
Uncoated Tablets	DIS	Water	DIS	Water
Film Coated			DIS	Water
Plain Coated Tablets (other than Film Coated)	DIS	Water	PCT	Water
Sublingual Tablets	DIS	Water	⊕	-
Buccal Tablets	DIS	Water	⊕	-
Chewable Tablets	⊕	⊕	⊕	-
Modified Release Tablets	-	-	-	-
Delayed Release Tablets	DRT	SGF / SIF	DRT	SGF / SIF
Hard Shell Capsules	DIS + WM	Water	DIS + WM	Buffer 4.5
Soft Shell Capsules	DIS + WM	Water	RUP	Water

DIS = Disintegration Test Apparatus A or B
 PCT = Plain Coated Tablets Test
 RUP = Rupture test
 DRT = Delayed Release Tablets Test
 WM = Wire Mesh to cover top of apparatus A
 ⊕ = not listed
 ⊕ = scientifically justified to be considered for disintegration tests

Beaker specifications

and distance of the bottom wire mesh of Apparatus A in the USP,
European Pharmacopeia and Japanese Pharmacopeia.

Apparatus A	USP 23 (701)	USP 26 (701/2040)	USP 30 (701/2040)	European Pharm. 2007 (5.8)	Japanese Ph. (14)
Volume of beaker (mL)	1000	1000	1000	1000	-
Height of beaker (mm)	142-148 (USP 23, suppl.9)	138-155	138-160	149±11	about 155
Diameter (inside, mm)	103-108 (outside) (USP 23, suppl.9)	97-110	97-115	106±9	about 110
Upward stroke: distance wire mesh/ surface (mm)	≥25	≥25	≥15	≥15	-
Downward stroke: distance wire mesh/ bottom (mm)	≥25	≥25	≥25	≥25	25

- ### Problems with current Specifications
- USP: The moving range of the basket-rack assembly should be between 53 and 57 mm
 - USP: the height of the basket from the bottom should be at least 25 mm and 15 mm from the top.
 - Math: This is a total height of 93 to 97 mm.
 - Taking the current beaker diameter specifications into account this adds up to a volume of between 687 and 1007 mL depending on the beaker diameter.
 - For 900 mL the medium height in a beaker with 115 mm diameter will only be 87 mm.
 - 900 mL will be too much in a 97 mm diameter beaker if the basket assembly should not be submerged.

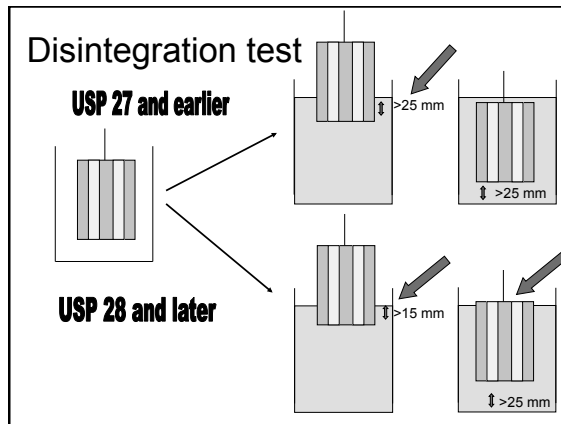
Disintegration study

Study design:

- Weight variation
- Performance uniformity (F- test)

Investigate influence of:

- Fixed volume in two beakers
- Fixed height of immersion volume



Disintegration test Study Design

USP 27 and earlier

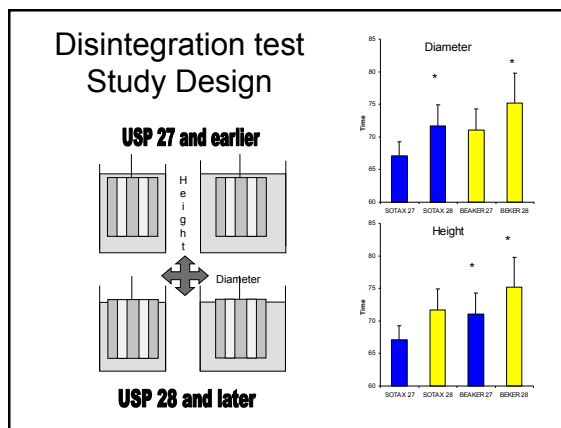
USP 28 and later

Two Beakers (diameter)

- SOTAX: narrow USP specification
- Fisher Sci 1.5 L larger than new USP specification

Two Conditions (height)

- USP 27
- USP 28



Study Results Small Beaker

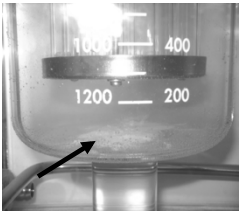
Before USP 28			Since USP 28		
Sotax run 1	Sotax run 2	Sotax run 3	Sotax run 1	Sotax run 2	Sotax run 3
67.4	67.1	65.0	66.3	74.2	71.3
67.6	69.4	63.1	77.0	71.2	69.0
64.6	66.6	67.3	72.4	69.4	67.4
62.2	68.2	67.5	74.4	74.4	71.1
66.3	69.4	68.4	77.3	73.3	68.2
68.5	71.1	68.2	72.4	73.1	68.4
66.1	68.6	66.6	73.3	72.6	69.2
2.3	1.7	2.1	4.0	1.9	1.6
		67.1			71.7
		2.2			3.2

Study Results Large Beaker


Before USP 28			Since USP 28		
1.5 L run 1	1.5 L run 2	1.5 L run 3	1.5 L run 1	1.5 L run 2	1.5 L run 3
72.3	73.2	68.1	74.4	72.3	74.3
73.3	79.6	70.3	83.4	70.3	70.4
70.0	68.0	73.0	83.0	73.4	70.5
70.2	68.4	76.3	77.6	75.4	70.2
70.4	67.3	71.4	75.2	77.4	79.1
68.4	70.3	68.6	81.1	78.1	68.0
70.8	71.1	71.3	79.1	74.5	72.1
1.8	4.6	3.1	3.9	3.0	4.0
		71.1			75.2
		3.2			4.6

1.5 L Beaker vs. Sotax

- 1.5 L Beaker



- Sotax Beaker



Summary

- All disintegration tests are statistically different when compared for diameter or medium height
- Are the differences relevant?

Sotax 27 67.1	Sotax 28 71.7
↕	
Beaker 27 71.1	Beaker 28 75.2

Proposed Tests

<701> Apparatus A Apparatus B	<2040> Apparatus A Apparatus B	<701>, <2040> Rupture test
- uncoated tablets	- uncoated tablets	- soft shell capsules
- plain coated tablets	- plain coated tablets	
- film coated tablets	- film coated tablets	
- sublingual tablets	- sublingual tablets	
- buccal tablets	- buccal tablets	
- delayed release tablets	- delayed release tablets	
- hard gelatin capsules	- hard gelatin capsules	
- hypromellose capsules	- hypromellose capsules	
- chewable tablets	- chewable tablets	

New Study according to USP 31

- Custom made tablets using a Calcium Acetate mineral mixture were produced
 - Apparatus B (1160 mg) Caplet
 - Apparatus A (200 mg) Biconvex tablet
- Beaker
 - Sotax (small)
 - Fisher 1 L
 - Fisher 1.5 L (JP size)
 - USP 31 conditions

Apparatus B

Sotax	1L	JP
25.2 min	27.8 min	36.7 min
± 0.4	± 0.4	± 1.5

Apparatus A

Sotax	1L	JP
43.4 min	NA	43.8 min
± 2.7	NA	± 2.9

These tablets in Apparatus B:
 Sotax: 41.5 ± 1.3
 JP: 49.8 ± 2.0

Conclusions

- The pilot study used surface erodable tablets
- Beaker sizes have different impact on test results in Apparatus A and B
- Apparatus B is sensitive to beaker size
- Apparatus A is not sensitive to beaker size

Recommendations

- Future study:
- Investigate surface erodabel tablets vs. disintegrating tablets

Possible study design:

make erodable tablets and use the same powder mix and add disintegrant to it.

Make large and small tablets from both mixtures and test them in Apparatus A and B with different Beakers.