FORMULATION DEVELOPMENT AND EVALUATION

Formulation Design

• Art, History, Trial and Error
  – Modifications of Proven Formulations with NCE
  – Typical Approaches for Solid Dosage Forms
  – Decision Tree Logic

• Expert Systems
  – Capsugel System

• Artificial Intelligence
  – Decision Tree Logic with AI
  – Multivariant Approaches
FORMULATION DEVELOPMENT AND EVALUATION

Formulation Design

• Definition of Dosage Form

• Definition of Product Composition

• Definition of Pharmaceutical Process

• Definition of In-Process Controls

• Definition of Product Specifications

• Definition of Product Packaging and Shipping
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Design

Water Insoluble Injectable Compound

• Solubilization
  – pH adjustment
  – Surfactant
  – Cosolvent
  – Complexation
  – Lipid system

• Suspension
  – Suspension
  – Nanosuspension
  – Emulsion
  – Microemulsion
## Formulation Design

### Dry Blend Capsule Formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Excipient Class</th>
<th>Size 1 Capsule</th>
<th>Size 0 Capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage Composition</td>
<td></td>
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<tr>
<td>Drug</td>
<td>40</td>
<td>10</td>
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<td>Lactose</td>
<td>Filler/Diluent</td>
<td></td>
<td>74</td>
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<td>Dibasic Calcium Phosphate</td>
<td>Filler/Diluent</td>
<td>53</td>
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<td>Microcrystalline Cellulose</td>
<td>Filler/Diluent/Wicking Agent</td>
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<td>15</td>
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<tr>
<td>Crospovidone</td>
<td>Disintegrant</td>
<td>4</td>
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<tr>
<td>Silicon Dioxide</td>
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<td>1</td>
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<tr>
<td>Magnesium Stearate</td>
<td>Lubricant</td>
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<td>Total Fill Weight, mg</td>
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<td>340</td>
<td></td>
</tr>
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</table>
# FORMULATION DEVELOPMENT AND EVALUATION

## Formulation Design - Tablet Formulations

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Excipient Class</th>
<th>Wet Gran.</th>
<th>Wet Gran.</th>
<th>Direct Comp.</th>
<th>Direct Comp.</th>
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<tr>
<td>Drug</td>
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<td>67</td>
<td>67</td>
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<td>10</td>
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<td>Povidone</td>
<td>Binder</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Sodium Starch Glycolate</td>
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<td>4</td>
<td>2</td>
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<tr>
<td>Croscarmellose Sodium</td>
<td>Disintegrant</td>
<td></td>
<td></td>
<td>2.5</td>
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<tr>
<td>Microcrystalline Cellulose coarse</td>
<td>Filler/Diluent/ Wicking Agent</td>
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</tr>
<tr>
<td>Sodium Starch Glycolate</td>
<td>Disintegrant</td>
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<tr>
<td>Silicon Dioxide</td>
<td>Glidant</td>
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<td>1</td>
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<td>0.5</td>
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<tr>
<td>Total Core Weight, mg</td>
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<td>450</td>
<td>450</td>
<td>480</td>
<td>200</td>
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</tbody>
</table>
# FORMULATION DEVELOPMENT AND EVALUATION

## Roller Compaction Formulation Design DOE

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Excipient Class</th>
<th>Roller Comp. A</th>
<th>Roller Comp. B</th>
<th>Roller Comp. C</th>
<th>Roller Comp. D</th>
<th>Wet Gran.</th>
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<tr>
<td>DRUG</td>
<td></td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>60</td>
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<tr>
<td>HPMC</td>
<td>Binder</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>MCC</td>
<td>Filler/Diluent</td>
<td>12</td>
<td>17</td>
<td>24</td>
<td>23.25</td>
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</tr>
<tr>
<td>DCP</td>
<td></td>
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<td>21.5</td>
<td>16.5</td>
<td>22.75</td>
<td>27.5</td>
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<td>3</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
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<tr>
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<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
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<td>3</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>Poloxamer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Lubricant</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
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<tr>
<td>Hydrogenated Castor Oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic Acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>DCP</td>
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<td>12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Crospovidone</td>
<td>Disintegrant</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>Glidant</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>SLS</td>
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<td>1</td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Poloxamer</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
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<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Hydrogenated Castor Oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stearic Acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Total Core Weight, mg</td>
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<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>350</td>
</tr>
</tbody>
</table>

**Note:** The above table shows the formulation design for roller compaction, where different excipients are used for different components (A to D) and wet granulation. The formulations include a range of excipients such as binders, disintegrants, glidants, lubricants, and other components to achieve the desired properties for compaction and granulation.
FORMULATION DEVELOPMENT AND EVALUATION
Solubilization Strategies

Injectable Formulation

START

Water-soluble?

Yes

No

Can a salt be made?

Yes

No

Log P

Low

High

Dose

High

Low

Melting Point

Low

High

Suitable Molecular Shape?

Yes

No

pH Adjustment
Salt Formation

Cosolvents

Inclusion Complexes

Nanosuspensions

Cosolvents
Micellar Dispersions
Emulsions
Other Lipid Systems

Increasing drug polarity

Suitable Molecular Shape?

Yes

No

Log P

Low

High

Dose

High

Low

Melting Point

Low

High

Can a salt be made?

Yes

No

Water-soluble?

Yes

No

START
FORMULATION DEVELOPMENT & EVALUATION Taste Masking

Active Pharmaceutical Ingredient

- Low dose
- Water insoluble
- Suspension layering

- High dose
- Water Sensitive
- Yes
- Alcohol
- Wet Granulation

- High dose
- Water sensitive
- No
- Water
- Wet Granulation

- Large particles
- High dose
- Dry granulation

- Low dose
- Water soluble
- Solution Layering

Fluid Bed Coating with conventional polymers

Taste masked active particles
FORMULATION DEVELOPMENT AND EVALUATION

Formulation Design

Model Expert System

CAPEX

Guo, M., et. al., Pharm. Tech., 26(9), 2002, p. 44 - 60
FORMULATION DEVELOPMENT AND EVALUATION

DOSAGE FORM EVALUATION

• In-Vitro
  – Physical/Chemical Stability
  – Processing
  – Dissolution (Discriminating, Biorelevant, IVIVC)

• In-Vivo
  – Pharmacokinetics
FORMULATION DEVELOPMENT AND EVALUATION

In-Vitro Evaluation

Granule Properties
(3% Binder Level)

Comparing Granulations using Kollidon 30 and Kollicoat IR

<table>
<thead>
<tr>
<th>Screen Size</th>
<th>20</th>
<th>40</th>
<th>80</th>
<th>120</th>
<th>200</th>
<th>325</th>
<th>Fines</th>
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<tr>
<td>% Weight Retained</td>
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<tr>
<td>3% Kollidon 30</td>
<td>0.00</td>
<td>10.00</td>
<td>40.00</td>
<td>20.00</td>
<td>10.00</td>
<td>3.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3% Kollicoat IR</td>
<td>0.00</td>
<td>5.00</td>
<td>25.00</td>
<td>15.00</td>
<td>15.00</td>
<td>3.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Evaluation - Homogenization

- Carbamazepine raw material
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Dissolution - Method Development, pH Effects

% Theophylline Released vs Time, min

pH = 1.5
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Dissolution - Method Development, pH Effects

% Theophylline Released

pH = 7.0

Time, min
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Dissolution

Capsules (50mg) dissolution at pH 6.8+0.1% SLS
n=2

% Dissolved

Time (min)

0 10 20 30 40 50 60

0 20 40 60 80 100 120

20% dog capsules
30% dog capsules
CSF capsules

30% ME capsule 1
30% ME capsule 2
20% ME capsule 1
20% ME capsule 2
CSF capsule 1
CSF capsule 2

NOVARTIS
Dissolution of 20% melt extrusion (pH2, non-sink) after 1 month storage

n=3

Dissolution Stability

- 1 month 25C/60%RH closed
- 1 month 40C/75%RH closed
- Initial analysis of dog capsules
- End analysis of dog capsules (1 month ambient)
FORMULATION DEVELOPMENT AND EVALUATION
In-Vivo Evaluation

- High pH solution and IDD™ formulation display identical IV-PK profile

GW Pace et al.; Pharm. Tech. (March 1999)
MA Clement et al.; The Pharmacologist 34(3), 204 (1992)
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Evaluation

Compression Profile

Compression Force Vs Ejection Force

Ejection Force (N)

Compression Force (kN)

- Kollidon 30
- Kollicoat IR
FORMULATION DEVELOPMENT AND EVALUATION
In-Vitro Evaluation

Compression Profile - Hardness

Compression Force Vs Hardness

Compression Force (kN)

Hardness (Kp)

Kollidon 30
Kollicoat IR

NOVARTIS
FORMULATION DEVELOPMENT AND EVALUATION

In-Vitro XRPD

No difference in crystal structure before and after homogenization
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Evaluation in Dogs

![Graph showing mean plasma concentration over time for different formulations and controls.](image-url)
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Evaluation in Dogs
FORMULATION DEVELOPMENT AND EVALUATION
Formulation Evaluation in Dogs

![Graph showing concentration vs. time for different formulations and control.](image-url)
FORMULATION DEVELOPMENT AND EVALUATION
OraVescent™ Fentanyl - Buccal 30 minutes

Plasma Conc. (ng/ml) vs Time (min)

- Actiq®
- Non-effervescent
- OraVescent Buccal
FORMULATION DEVELOPMENT AND EVALUATION
OraVescent™ Fentanyl - Sublingual vs. Buccal 12 hours
FORMULATION DEVELOPMENT AND EVALUATION
OraVescent™ Fentanyl - Buccal 12 hours

Plasma Conc. (ng/ml) vs Time (hr)

- Actiq®
- Non-effervescent
- OraVescent Buccal
FORMULATION DEVELOPMENT AND EVALUATION
Animal Pharmacokinetics

Mean PK profiles (n=4)
FORMULATION DEVELOPMENT AND EVALUATION
Estimated Oral Bioavailability by Cross Study Comparison

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Estimated Absolute Oral Bioavailability (% ± SD)</th>
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<tbody>
<tr>
<td>Control</td>
<td>7.6 ± 4.7</td>
</tr>
<tr>
<td>Formulation #1</td>
<td>19.9 ± 8.8**</td>
</tr>
<tr>
<td>Formulation #2</td>
<td>35.3 ± 10.6</td>
</tr>
<tr>
<td>Formulation #3</td>
<td>27.8 ± 21.7</td>
</tr>
</tbody>
</table>
FORMULATION DEVELOPMENT AND EVALUATION
Pharmacodynamics

- Dantrolene – skeletal muscle relaxant administered during anesthesia
- Very low volume and rapid IV administration possible

![Graph showing temperature change over time after intravenous injection of IDD-P™ Dantrolene.](chart)

Karan et al.; *Anesthesiology* 79(3A), 437 (1993)
FORMULATION DEVELOPMENT AND EVALUATION

Inhalation Delivery Systems

- pressurized Metered Dose Inhaler (pMDI)
- Dry-powder inhaler (DPI)
- Nebulizer
FORMULATION DEVELOPMENT AND EVALUATION

**pMDI**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Portable</td>
<td>• Patient coordination problems (i.e. press and breathe)</td>
</tr>
<tr>
<td>• Apparently Easy to Use/convenient</td>
<td>• Cold Freon effect</td>
</tr>
<tr>
<td>• Remaining Product Is Uncontaminated</td>
<td>• High oropharyngeal deposition</td>
</tr>
<tr>
<td>• Tamper-proof</td>
<td>• No dose counter</td>
</tr>
<tr>
<td>• Protects Drug from Light, O₂ and H₂O</td>
<td>• Phase-out of CFCs</td>
</tr>
<tr>
<td>• Multiple Dose</td>
<td>• Complex patent situation</td>
</tr>
<tr>
<td>• Accurate Dose Metering</td>
<td>• lower dose limitation cf DPIs</td>
</tr>
<tr>
<td>• High Respirable Fraction</td>
<td></td>
</tr>
<tr>
<td>• Inexpensive</td>
<td></td>
</tr>
<tr>
<td>• Mature Technology / Established Vendors (&gt; 40 years)</td>
<td></td>
</tr>
</tbody>
</table>
### Dry Powder Inhalers

#### Advantages
- Convenient portable devices
- Dose counter on most
- Easy to use
- No propellants
- Breath activated (no coordination problems)
- Higher drug payloads

#### Disadvantages
- Flow rate dependent performance
- Moisture protection required
- More expensive than pMDIs
- Can be awkward to load
- Not suitable infants
**Nebulizers**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No coordination required</td>
<td>• Long treatment times, Heating</td>
</tr>
<tr>
<td>• Dosing using normal tidal breathing</td>
<td>• Bulky, inconvenient and complex to use</td>
</tr>
<tr>
<td>• All age groups</td>
<td>• Expensive to manufacture</td>
</tr>
<tr>
<td>• Acute care</td>
<td>• Erratic performance (variability)</td>
</tr>
<tr>
<td></td>
<td>• High drug wastage (poor efficiency)</td>
</tr>
<tr>
<td></td>
<td>• Prone to microbiological contamination</td>
</tr>
<tr>
<td></td>
<td>• Poorly regulated, nebulizer is sold independently of drug solution</td>
</tr>
</tbody>
</table>
FORMULATION DEVELOPMENT AND EVALUATION
DPI - Formulations

- Adhesive forces between drug and carrier particles should also be sufficient to prevent segregation during transport and storage
- **Carrier factors** that affect DPI efficiency:
  - Particle size distribution, surface, charge
- **Drug substance** factors that affect DPI efficiency:
  - Particle size, surface, shape, charge, hygroscopicity, drug/carrier ratio, crystallinity, physical stability of crystalline/amorphous form
- Other formulation approaches for DPIs
  - Crystal engineering of DS using supercritical fluids
  - Use of ternary components
  - Spray drying processes for sensitive biomolecules
Majority of DPI formulations comprise of micronized drug mixed with an inert carrier (usually lactose) as a bulking agent, to aid processability and manufacturing (flowability filling into devices/packaging materials) and to enhance fluidisability during inhalation.

- Adhesive forces between drug and carrier particles are the most critical parameter that determines the degree of redispersion of micronized primary particles in the inspired air stream.
FORMULATION DEVELOPMENT AND EVALUATION

pMDI Formulations

• Surfactant
  - lecithin, sorbitan trioleate, oleic acid
  - aids wetting of DS during blend manufacture
  - stabilization of drug particles against coagulation and/or rapid flocculation
  - aid solubilization of DS for solution formulations
  - valve lubrication/functionality

• Co-solvent
  - ethanol to solubilize surfactants
  - reduce vapour pressure

• Active Substance (DS)
  - suspended or in solution depending on solubility in p-mixture (salt forms)
  - particle size reduction by micronization (90% < 5µm, 0% > 10µm)
  - chemical stability in p-mixture
  - physical stability in p-mixture (polymorphic changes, solvate formation, crystal growth from Ostwald ripening)
FORMULATION DEVELOPMENT AND EVALUATION
pMDI Container Closure Systems

• Container
  Aluminium alloy, coatings (stability) or glass

• Valve
  Available in different metering volumes (25, 50, 63 and 100µl), suppliers and components mechanical stability over shelf life

• Actuator
  Available range, colors, shapes and sizes
  Extension of valve stem
  Geometry affect characteristics of aerosol plume
# FORMULATION DEVELOPMENT AND EVALUATION - pMDI

<table>
<thead>
<tr>
<th>Formulation</th>
<th>%Excipient</th>
<th>Excipients</th>
<th>% Co-solvent</th>
<th>Flocculation</th>
<th>Settling Onset</th>
<th>Settling Time</th>
<th>Comments</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>none</td>
<td>0</td>
<td>&lt;10 secs</td>
<td>20 secs</td>
<td>3 mins</td>
<td>drug deposition on walls</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>none</td>
<td>15% Ethanol</td>
<td>&lt;10 secs</td>
<td>30 secs</td>
<td>3 mins</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>none</td>
<td>15% IPA</td>
<td>10 secs</td>
<td>25 secs</td>
<td>2 mins</td>
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</tr>
<tr>
<td>4</td>
<td>0.03</td>
<td>Oleic Acid</td>
<td>5% Ethanol</td>
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<td>20 secs</td>
<td>3 mins</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.03</td>
<td>Span85</td>
<td>15% Ethanol</td>
<td>&lt;10 secs</td>
<td>20 secs</td>
<td>2.5 mins</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.03</td>
<td>Oleic Acid</td>
<td>5% IPA</td>
<td>&lt;10 secs</td>
<td>20 secs</td>
<td>3 mins</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.03</td>
<td>Span85</td>
<td>15% IPA</td>
<td>&lt;10 secs</td>
<td>20 secs</td>
<td>3 mins</td>
<td></td>
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<tr>
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<td>20 secs</td>
<td>&gt;5 mins</td>
<td>&gt;5 mins</td>
<td>drug deposition on walls</td>
</tr>
<tr>
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<td>0</td>
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<td>15% Ethanol</td>
<td>12 secs</td>
<td>1 min</td>
<td>&gt;5 mins</td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>none</td>
<td>15% IPA</td>
<td>12 secs</td>
<td>1.5 mins</td>
<td>&gt;5 mins</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.03</td>
<td>Oleic Acid</td>
<td>5% Ethanol</td>
<td>10 secs</td>
<td>&gt;5 mins</td>
<td>&gt;5 mins</td>
<td></td>
</tr>
<tr>
<td>12</td>
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<td>Span85</td>
<td>15% Ethanol</td>
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<td>4 mins</td>
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<tr>
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<td>&gt;5 mins</td>
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<td>1 min</td>
<td>&gt;5 mins</td>
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