Dissolution testing of non-conventional dosage forms

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Annual Symposium for Technical Services
27th Sept 2011

Rationale for dissolution testing

- Purpose of dissolution test
  - Product development
    - Investigational formulations testing (QC)
  - Product evaluation
    - Stability program (QC)
    - Establishment of product's shelf life
    - Release of commercial batches (QC)
  - SUPAC changes
    - IVIVC development

- A dissolution method developed solely for QC for manufacturing without bearing on patient safety or product efficacy has limited use

Dissolution for IVIVC

- Establishment of IVIVC and its ability to discriminate requires good design
- Reproduce conditions in GI after dosage form administered as closely as possible
- Very often, the in vitro dissolution test is found to be more sensitive and discriminating than the in vivo test

Practicality of testing

- Balance between conditions allowing for release over appropriate timeframe (for QC applications)
- General principles of dissolution tests for conventional oral dosage forms also apply to the in vitro release tests for alternative dosage forms
  - not possible to have a single test system that could be used to evaluate the release characteristics of all novel products
  - Need to look at requirements on individual and possibly case-by-case basis

Apparatus 3

- Reciprocating cylinder
- Useful for modified release dosage forms
- Can change dissolution medium to simulate changes in environment through GI tract
Flow-through cell

- Disk assembly method
- Cell method
- Rotating cylinder method
- USP 5,6&7 Paddle over disk, cylinder method, reciprocating disk

The disc comprises a 35 mm o.d. sieve having a pore size of 125 microns mounted in a stainless steel holder having a diameter of 41.2 mm and is designed to hold the transdermal patch at the bottom of the vessel.

Transdermal patch testing

- Fentanyl formulations
  - Fentals®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, Victanyl®
  - Media pH-5 to 6
  - Media Temperature-32 ºC
  - Paddle Speed : 100 rpm
  - 6-12 samples

Patch formulation

- Rate-limiting step for matrix patches is normally the skin
- More likely to get relevant IVIVC data for reservoir

Franz diffusion cell

- Rate-limiting step for matrix patches is normally the skin
- More likely to get relevant IVIVC data for reservoir

Media composition

<table>
<thead>
<tr>
<th>FaSSGF</th>
<th>FeSSGF (middle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate [µM]</td>
<td>Sodium chloride [mM]</td>
</tr>
<tr>
<td>80</td>
<td>237.02</td>
</tr>
<tr>
<td>Lecithin [µM]</td>
<td>Acetic acid [mM]</td>
</tr>
<tr>
<td>20</td>
<td>37.12</td>
</tr>
<tr>
<td>Pepsin [mg/mL]</td>
<td>Sodium acetate [mM]</td>
</tr>
<tr>
<td>0.4</td>
<td>29.75</td>
</tr>
<tr>
<td>Sodium chloride [mM]</td>
<td>Milk/buffer</td>
</tr>
<tr>
<td>34.2</td>
<td>1:1</td>
</tr>
<tr>
<td>HCl [µL]</td>
<td>HCl [µL]</td>
</tr>
<tr>
<td>pH 1.6</td>
<td>pH 5</td>
</tr>
</tbody>
</table>

Jantratid E, Dressman J. Biorelevant Dissolution Media, Dissolution Technologies, August 2009
### Simulated fluid

<table>
<thead>
<tr>
<th>FeSSIF-V2 (mM)</th>
<th>FaSSIF-V2 (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate: 3</td>
<td>Sodium taurocholate: 10</td>
</tr>
<tr>
<td>Lecithin: 0.3</td>
<td>Lecithin: 2</td>
</tr>
<tr>
<td>Maleic acid: 19.12</td>
<td>Glycerol monoleate: 5</td>
</tr>
<tr>
<td>Sodium hydroxide: 34.8</td>
<td>Sodium oleate: 0.8</td>
</tr>
<tr>
<td>Sodium chloride: 66.82</td>
<td>Sodium hydroxide: 34.8</td>
</tr>
<tr>
<td>pH: 6.5</td>
<td>Sodium chloride: 125.5</td>
</tr>
<tr>
<td>pH: 5.8</td>
<td></td>
</tr>
</tbody>
</table>

### Duration of dissolution study

- Drug absorbed from upper SI, administered in fasted state - duration of 30 minutes
- Drug absorbed throughout SI and LI, administered with food - duration of 10 hours
- More usual
  - gastric conditions: 15-30 mins
  - SI conditions: 1h

### Fibre optic dissolution

- Direct measurement of dissolved drug in the dissolution vessel via an individual probe for each dosage unit tested
  - *In situ* measurements
  - profiles are calculated in real time
- More samples can be taken in shorter time
  - Useful for fast dissolving formulations

### Manual vs. fibre optic

- More samples can be taken in shorter time
  - Useful for fast dissolving formulations

### Apparatus used for special dosage forms

<table>
<thead>
<tr>
<th>Type of dosage form</th>
<th>Oral suspensions</th>
<th>Paddle</th>
<th>Orally disintegrating tablets</th>
<th>Paddle and disintegration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chewable tablets</td>
<td>Basket, paddle, reciprocating cylinder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosols</td>
<td>Cascade impactor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin dissolvable films</td>
<td>Basket and disintegration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal delivery patches</td>
<td>Paddle over disk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical semisolids</td>
<td>Franz diffusion cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppositories</td>
<td>Paddle, modified basket, dual chamber flow-through</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powders and granules</td>
<td>Flow-through cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microparticulates</td>
<td>Modified flow-through cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implants</td>
<td>Modified flow-through cell</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chewing gum</td>
<td>Special apparatus (Ph. Eur)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Method development

- Avoid unnecessary proliferation of test equipment
  - First approach should use compendial equipment
- Well developed for suspensions, chewable tablets, suppositories, topicals etc
- Some dosage forms, such as chewing gums, powders, and parenterals, further method development and refinement is needed
Dosage forms for oral cavity

- Local, sublingual or buccal
  - convenient, accessible, and generally well accepted
- Can avoid first pass metabolism and presystemic metabolism
- Can have rapid onset

Medicated chewing gums

- Medicinal chewing gums have been available since the late 1920s (Aspergum®)
  - Nicotine Chewing Gums
    - Nicotine Polacrilex USP. The nicotine is loaded to around 18% w/w on an ion exchange resin (Amberlite™ IRA964)
    - include water-soluble buffering agents such as alkali carbonates to increase the salivary pH and thereby increase bioavailability.

Advantages of chewing gum-based drug delivery

- Convenient and discreet
- Widely acceptable
- Fast acting
- Suitable for prolonged-release applications
- Suitable for local and systemic applications

Typical gum formulation

- Gum base 29%  
  - elastomer, plasticiser, texture agent, wax, lipid, emulsifier, colorant, antioxidant
- Sorbitol 43%
- Sorbitol solution 21%
- Glycerin 5%
- Peppermint flavour 1%
- Lecithin 0.5%
- Aspartame 0.33%

Manufacture of chewing gums

- use conventional gum processes
- The gum base is softened or melted and placed in a kettle mixer where sweeteners, syrups, active ingredients and other excipients are added at a defined time
- The gum is then sent to a series of rollers that form it into a thin, wide ribbon.
- Coated with an anti-sticking agent can be added (e.g. magnesium stearate, calcium carbonate, or finely powdered sugar or sugar substitute)
- Finally, the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity.

Chewing gum formulations

- The mechanism and kinetics of release not yet been completely understood due to the complex nature of the formulation
- Release conventionally measured by chew-out studies
  - Need to control how gum is chewed
  - Process is destructive at each timepoint, cannot sample
- Need for a in vitro test apparatus
Chewing gum apparatus

- Chewing apparatus adopted by EP in 2000

The chewing machine

- Temperature-controlled chewing chamber
  - the gum piece is chewed by two electronically-controlled horizontal pistons driven by compressed air
- Pistons transmit twisting and pressing forces to the gum whilst, a third vertical piston, (“tongue”) operates alternately to the two horizontal pistons to ensure that the gum stays in the appropriate position
- Temperature can be maintained at 37°C±0.5°C and the chew rate varied
- Other adjustable settings include the volume of the medium, distance between the jaws and the twisting movement
- The EP recommends using 20 mL of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 mL and a chew rate of 60 strokes per minute

Selection of dissolution medium

Artificial saliva

<table>
<thead>
<tr>
<th>Components of artificial saliva</th>
<th>Quantity (mmol L(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{KH}_2\text{PO}_4)</td>
<td>2.5</td>
</tr>
<tr>
<td>(\text{Na}_2\text{HCO}_3)</td>
<td>2.4</td>
</tr>
<tr>
<td>(\text{KHCO}_3)</td>
<td>15.0</td>
</tr>
<tr>
<td>(\text{NaCl})</td>
<td>10.0</td>
</tr>
<tr>
<td>(\text{MgCl}_2)</td>
<td>1.5</td>
</tr>
<tr>
<td>(\text{CaCl}_2)</td>
<td>1.5</td>
</tr>
<tr>
<td>Citric acid</td>
<td>0.15</td>
</tr>
<tr>
<td>pH adjusted to 6.7 with NaOH or HCl</td>
<td></td>
</tr>
</tbody>
</table>
Release from commercial products

Directly compressible gumbases

- As the heating process involved in conventional methods may limit the applicability of the process for formulation of thermally labile drugs, directly compressible, free-flowing powdered gums have been developed to simplify the process
- Mixtures of polyol(s) and/or sugars with a gum base
- These formulations can be compacted into a gum tablet using a conventional tablet press, thus enabling rapid and cheap development of a gum delivery system

Directly compressible bases

Process parameters

- Influence of chew rate on commercial 2 mg gum

General conclusions

- As a general rule, under sink conditions, the rate at which the drug is released is directly proportional to the chewing frequency and aqueous solubility of drug substance and is indirectly proportional to the mass of the gum base
- Order of addition of excipients and mixing efficiency have impact on release
In vitro chew rate study (4 mg)

Chew out study

- Single-centre, open-label, four-phase cross-over design with a minimum interval of 24 hours between each phase.
- 4 mg branded gum using a standard chewing protocol for the prescribed time period of 2, 5, 7, 10, 15, 20, 25 and 30 minutes
- The gum was chewed once every 4 seconds, accompanied by an audible sound

Chew out study methodology

- Chewed for 30 seconds on one side of the mouth and then moved the gum to the other side of the mouth, alternating the side of the mouth every 30 seconds
- Subjects were instructed to swallow at verbal command every 30 seconds
- At the end of the chew interval, each chewed gum piece was collected and analysed for any residual nicotine.

Correlations

Summary

- Need a range of different dissolution apparatus for testing of novel dosage forms
  - shows promise for other dosage forms, such as chewable tablets, suspensions, and suppositories.
- For others, need to consider the application
  - Potential to provide information regarding the in vivo release
  - Need further development and refinement for routine QC applications
- Have defined relationship with in vivo data for chewing apparatus