Biorelevant In-Vitro Release Testing of Non-Oral Dosage Forms – FDA Perspectives

Tapash Ghosh, Ph.D

Team Leader, Biopharmaceutics, ONDQA, FDA

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Outline

- Background
- Product Specific/Release Testing
- Examples
- Comments and Summary

What is Biorelevant Release Test?

- A bio-relevant release test is an *in-vitro* test which is conducted using experimental conditions which provide useable surrogate for the corresponding *in-vivo* environment
- capable of predicting blood concentration - time profiles obtained from the human PK studies.

Biorelevant Release Test : Expectations

– Should be conducted using appropriate and bio-relevant experimental conditions

- so that the same in vitro predictions occur in terms of rank order and relative degree as would be seen in vivo as changes are made to the drug product.
- absolute values are not important.
- use of non-physiological test are to be avoided

Biorelevant Release Test : Expectations

– Should be able to predict *in vivo* (blood) drug concentration-time profiles

- For example, the predicted profiles should at least be able to differentiate between fast (e.g. IR) and slow release (ER) products as these would be from an *in vivo* study.

Biorelevant Release Test : Expectations

– Such a test could then be used to evaluate potential drug release characteristics of a test product *in vivo*.

Background: In-Vitro Release Test

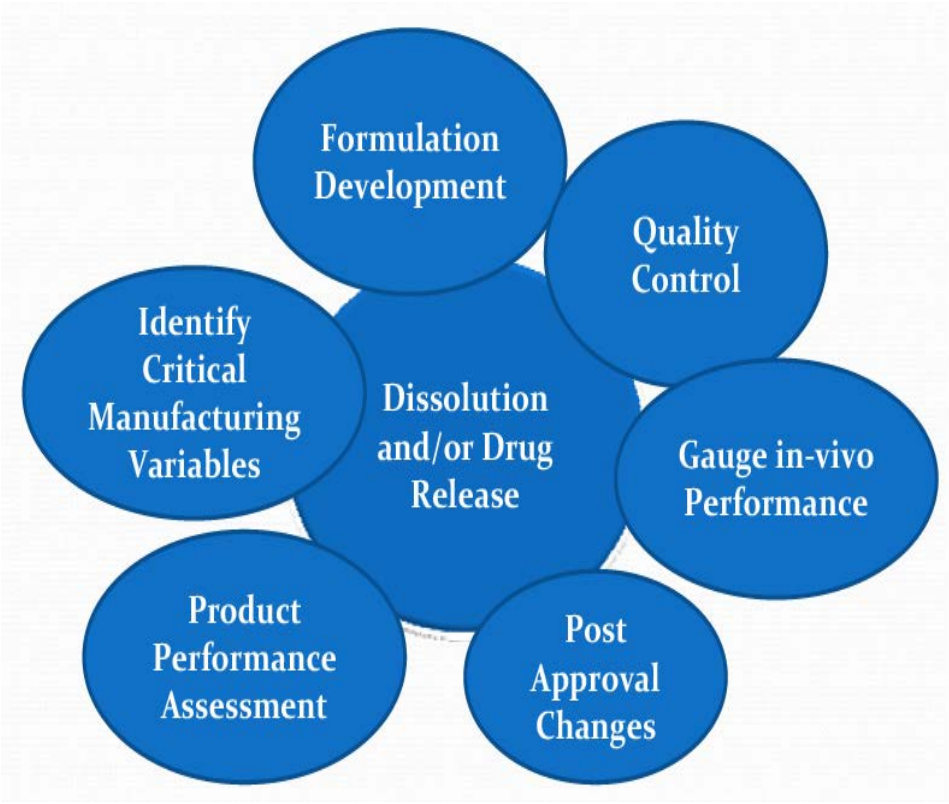
- An *in vitro* release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form.

- In most cases, the *in vitro* release rate is a useful attribute to assess product sameness between pre-change and post-change products.

A simple, reliable, and reproducible in vitro test is important:

- In initial product development
- to ensure batch-to-batch uniformity – a routine quality control test
- as it may be able to predict *in-vivo* performance especially for systemic use formulations
- as it may be used as a design space parameter in DOE in a QbD application

A simple, reliable, and reproducible in vitro test is important:



In Vitro Release Testing of Non-Oral Dosage Forms

- Method development may follow general principles of dissolution tests for solid oral dosage forms
- May be used for the biopharmaceutical characterization of the drug product, and
- May be used as a discriminating tool to assure consistent product quality within a defined set of specification criteria.

Development:Non-Oral Dosage Forms

Apparatus selection, composition of the dissolution medium, agitation (flow rate), and temperature be given appropriate consideration during method design keeping in mind:

– different characteristics of the novel/special dosage forms

– different sites and modes of administration

Release Testing Suggestions

- Orally Disintegrating or Orodispersible Tablets
- Chewable Tablets
- Transdermal Delivery Systems
- Semisolid Topical Dosage Forms
- Medicated Chewing Gum
- Suppositories
- Parenteral Dosage Forms: IV, IM and SC
- Inhalation Products/Aerosols
- Opthalmic Dosage Forms
- Implants
- Microparticulate, Nanoparticulate, and Liposome Formulations

Word of Caution

Discussion is based on information available in public domain! No endorsement is implied.

Orally Disintegrating or Orodispersible Tablets

- *In vitro* dissolution testing should follow the principles of solid oral dosage forms (tablets) or suspensions
- The rotating paddle may be the method of first choice
- A disintegration test may be used in lieu of a dissolution test if it is shown to be discriminating (ICH Q6A Decision tree 7).

Chewable Tablets

- Current test conditions are the same as used for conventional tablets of the same active pharmaceutical ingredient
- but because of the nondisintegrating nature of the dosage form, there may be a necessity to alter test conditions (e.g., increase the agitation rate) and specifications (e.g., increase the test duration).
- Therefore, it will be bio-relevant to mimic chewing (tablet breakup) somehow (maybe using some chewing apparatus) and then the same media and conditions could apply as for the regular (swallow) tablets.

Transdermal Delivery Systems

- Current compendial apparatus include the paddle over disk/disk assembly method (apparatus 5), the rotating cylinder (USP apparatus 6)
- The pH of the medium ideally should be adjusted to pH 5–6, reflecting physiological skin conditions.
- the test temperature is typically set at 32°C

Transdermal Delivery Systems

- The experimental setup (release medium, agitation speed, etc.) and testing time should take into account the amount of drug administered to the body and the application time of the patch

- In cases where drug release cannot be achieved in an appropriate time by using standard aqueous dissolution media, aqueous – organic solvent mixtures can also be used.

Semisolid Topical Dosage Forms

- FDA's SUPAC-SS Guidance for Industry describes the release rate studies using the vertical diffusion cell (Franz cell) procedure and requires in vitro release rate comparison between pre-change and post-change products for approval of SUPAC-related changes

- Previous presentation described the procedure in detail

Medicated Chewing Gum

- the intensity and frequency, with respect to the duration of the experiment, of shearing forces/activities (i.e., “chewing” action) can have a significant influence on drug release rate.

- The European Pharmacopoeia provides a description of a stainless steel three-piston apparatus, which is required for testing of “medicated chewing gums”

Medicated Chewing Gum

- The test is typically operated at 37°C and at 60 cycles per minute.
- Test media with a pH 6 are commonly used, since this pH corresponds to reported saliva pH values of 6.4 (adults) or 7.3 (children).

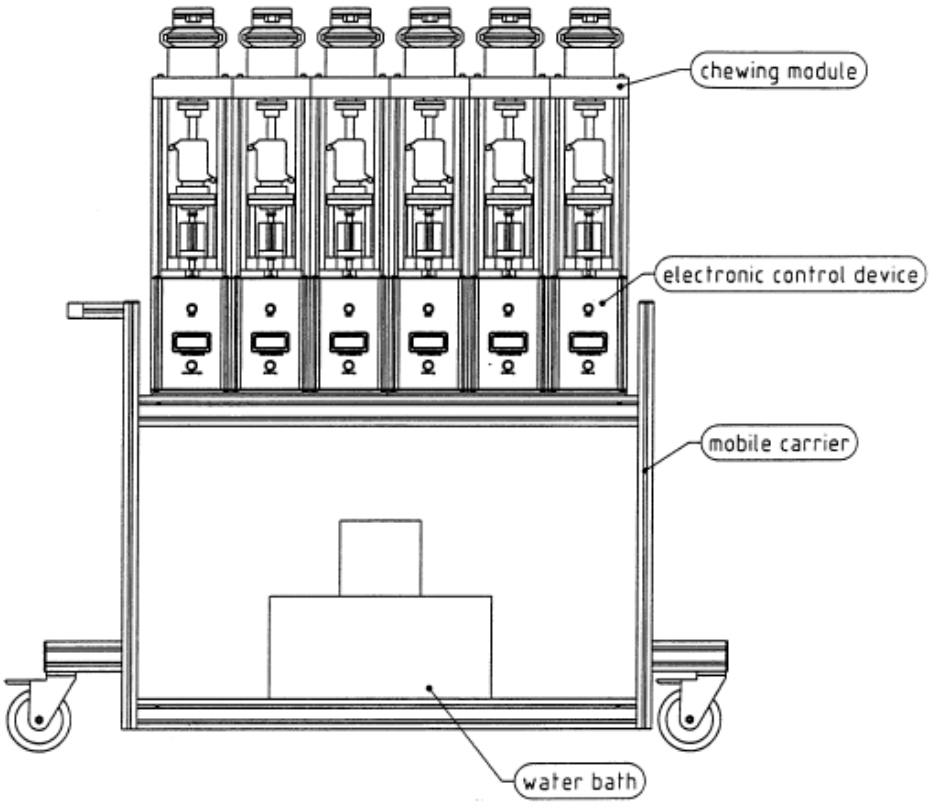
Medicated Chewing Gum

- A second apparatus based on a double piston and a double-walled dissolution vessel has also been proposed for inclusion in the Ph. Eur. as an alternate apparatus

- The standardization of jaws in order to mimic a chewing action *in vivo* remains one of the greatest challenges.

Technical drawing of a Chewing Apparatus

(IJP **189** (1999) 57–65)



Suppositories and Inserts

- A paddle method or continuous flow method are useful for the hydrophilic suppositories with product specific adjustment of parameters such as paddle rotating speed or flow rate of the medium

- Sink conditions should be taken into consideration in designing such a drug release testing method

Suppositories and Inserts

- A rotation speed of 50 rpm in the paddle method and a flow rate of 16 mL/min in the continuous flow method using a phosphate buffer pH 7.4 at 37°C can be used as a starting point in method development for such suppositories.
- For drug release testing of lipophilic suppositories, it is recommended in Ph. Eur. to employ continuous flow apparatus.
- Nevertheless, if reproducibility of test results is given, a basket or paddle apparatus can also be used.

Parenteral Dosage Forms: IV, IM and SC

- The *in vivo* conditions at the site of injection such as body temperature, metabolism, tissue pH, buffer capacity, level of exercise as well as the volume and osmolarity of the product are to be considered with regard to performance indicating drug release testing methods

- Since real-time methodology mimicking *in vivo* conditions take months for drug release to occur, special attention should be paid to evaporation and contamination of the media

Parenteral Dosage Forms: IV, IM and SC

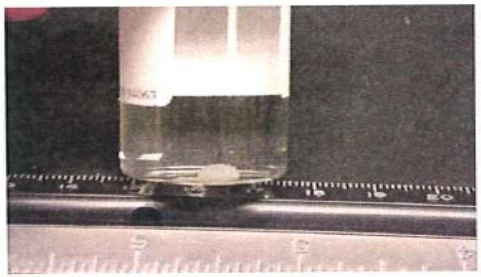
- Accelerated tests should have relevance to the real-time tests and should not alter the mechanisms of the drug release but only speed up the process.

- such a release method should be able to identify burst release from the formulation and also supply information about the duration of this phase for controlling the efficacy and safety of the product.

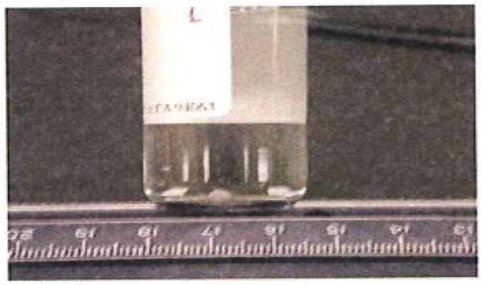
Parenteral Dosage Forms: IV, IM and SC

- In general, in vitro release of over 80% is desirable.
- Such a method can be developed through the modifications of pH, temperature, or physical agitation

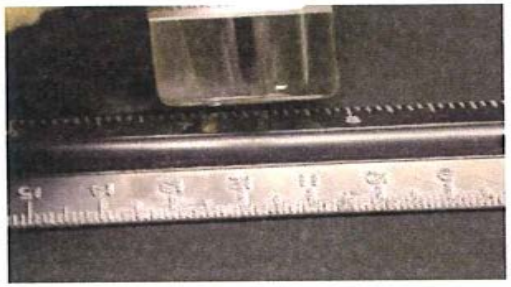
Representative In-Vitro release Morphology of a SC Parenteral



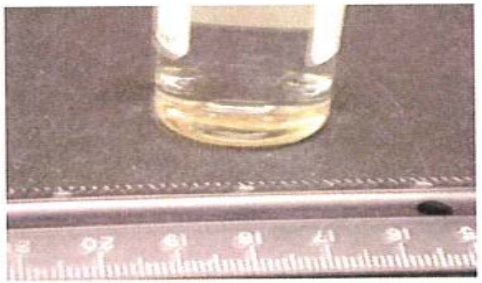
Beginning of Experiment



Middle of Experiment



Closer to the end of the Experiment



End of Experiment

Inhalation Products/Aerosols

- At present, there is no generally acceptable *in vitro* drug release test for inhalation aerosol drug products.
- Two most important criteria to assess performance of these products are (1) aerodynamic particle size distribution (APSD) and (2) uniformity of dose delivered.

Opthalmic Dosage Forms

- The development of unique tests, equipment, and specifications is frequently required for ophthalmic dosage forms.
- The utilization of appropriately modified instrumentation, techniques, and methods has resulted in vastly improved precision, formulation relevant sensitivity, and analytical sensitivity.
- A new chapter in USP <1771> under development suggests SUPAC
  - SS guidance recommendation for product performance test.

Implants

- a release mechanism ensures the amount of drug being delivered per time unit throughout their residence time in the body

- In cases where extended time requirements are necessary for real time experiments, mathematical models for extrapolation may be allowed.

Implants

- While accelerated methods may be acceptable for quality control purposes, the validation information should demonstrate that the selected test is discriminating and able to detect meaningful manufacturing changes.

Implants

- A relation between real time *in vitro* release and accelerated *in vitro* release data is encouraged and should apply when setting acceptance criteria for the quality control method

- An IVIVC may be developed to qualify certain pre- or post-approval CMC-related changes.

Microparticulate, Nanoparticulate, and Liposome Formulations

- The paddle apparatus, flow-through cell, and modified flow-through cell have been used successfully for these formulations.
- Static or rotating bottles have also been used for *in vitro* release testing.
- Possible alternatives to the standard paddle *in vitro* release test include utilization of the dialysis sac versus sample and separation.

Microparticulate, Nanoparticulate, and Liposome Formulations

- The composition of the medium should take into consideration the osmolarity, pH, and buffer capacity of the fluids at the site of administration, which are usually assumed to resemble that of plasma (or muscle) but with lower buffer capacity.

- the main challenges are to determine the appropriate duration of the test and the times at which samples are to be drawn in order to characterize the release profile adequately.

Microparticulate, Nanoparticulate, and Liposome Formulations

- accelerated test conditions are attractive – at elevated test temperatures and at pH values offering faster drug release
- however, accelerated release profile should be predictive of the real-time release profile.
- it should be biorelevant.

Microparticulate, Nanoparticulate, and Liposome Formulations

- It is accepted that the two release profiles should exhibit specific correlation in three time points: one early on, one in the middle of the release testing and one near the end (>80% cumulative release)

- Model-dependent approaches have also been suggested, where the real-time and accelerated data are compared following mathematical modeling

Comments

- In general, an in vitro dissolution/release test is expected for each novel/special dosage form - systemic or nonsystemic (e.g., topical semisolid dosage forms), for formulation development, for investigations to support post-approval changes and for batch-to-batch quality control.
- In vitro release methods should be relatively easy to perform and ideally should be predictive of in vivo release.

Comments

- If an *in vivo / in vitro* correlation (IVIVC) can be established, then the *in vitro* release profile obtained for different batches can be used to ensure product behavior *in vivo*
- If you anticipate this need, you are encouraged to discuss this with us beforehand. Accordingly, the FDA may grant a biowaiver for cases such as manufacturing site changes, raw material supply and instrument changes, quality control purposes and bioequivalence studies.

Comments

- It should be noted that it is not possible to develop an IVIVC for all drug products.

- specific formulation design and potential (physicochemical) interactions between the dosage form and the physiological environment at the site of administration are important factors

Comments

- also because of the necessary design of *in vitro* dissolution equipment for novel/special dosage forms, dissolution/release data *in vitro* may be artificially influenced by test or equipment parameters

- therefore potentially less predictable *in vivo* release than typically experienced for “conventional” dosage forms are possible.

Comments

- However, an *in vitro* release test can be developed which satisfies the requirements for batch release of product.

- Such *in vitro* release tests must be able to discriminate between in specification and out of specification batches and should demonstrate a complete or greater than 80% release of drug

Questions

- How do we decide how long to run an *in-vitro* test?
- How do we set *in-vitro* release specification/

In-Vitro Release Sampling Variation

Dosage	Duration	Sampling Times
IUD	3 years	24 hrs over 3 years
IUD	3 years	2, 11, and 25 days
IUD	1 year	1, 9, 17, and 30 days
Implant	28 days	7, 14, 17, 21 and 28 days

Summary

- FDA is a science based organization
- Promotes public health through scientific innovation
- New Drug Side – do not believe in a cookie – cutter approach
- Always looks for new method based on individual dosage form need

Summary

- Has to be properly developed and validated for scientific accuracy and reproducibility
- Do not hesitate to bring your idea and innovation to discuss with us
- We are there to be your partner to assure that quality medicines are available for the American public via regulation of pharmaceutical quality.

Selected References

- Brown, C.K., et al., FIP/AAPS Joint Workshop Report: Dissolution/In Vitro Release Testing of Novel/Special Dosage Forms. AAPS Pharmscitech, 2011. **12**(2): p. 782-794.

- Kastellorizios, M. and D.J. Burgess, In vitro drug release testing and in vivo/in vitro correlation for long acting implants and injections, in Long Acting Injections and Implants. 2012, Springer. p. 475-503.

- Kvist C., et. al., Apparatus for studying in vitro drug release from medicated chewing gums, International Journal of Pharmaceutics **189** (1999) 57–65

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49