Prague

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IN VITRO AND IN VIVO ASSESSMENT FOR LOZENGES

INTRODUCTION

Introduction

- Position of the problem
- What is requested in the guideline

Experiment

- Protocol
- Results

Outcome Conclusion

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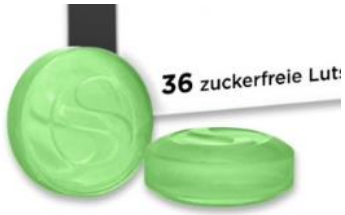
INTRODUCTION AND POSITION OF THE PROBLEM

WHY

1.4/10 mg
Cetylpyridinium Chloride
& Benzocaine



Lozenges deliver drugs locally for a local action

ONLY change is Excipient base

- Local acting actives

- Well established efficacy & safety

- No change to manufacturing

Alternate to in vivo equivalence ????

LEGAL BASIS

6. According to the state of the drug substance in the dosage form, e.g.:
…. b) Dissolved in a solid pharmaceutical form (e.g. lozenge);

In those cases where it is justified that the drug is released from the dosage form as a solution due to its high solubility and not as a suspension, it is possible to assess indirectly the local availability or the amount released by assessing the amount remaining in the dosage form at selected time points in an in vivo study. In addition, in those cases where it is justified that the drug is dispersed homogeneously in the dosage form, the amount remaining in the dosage form can be estimated by weight. Equivalence may be concluded as for in vitro dissolution tests as outlined in Appendix 1 of the 'Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)'. Dissolution profile similarity should be assessed based on an acceptance range of ±10% in accordance to the acceptance range (≥50) of the f2 similarity factor.

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract - Revision 1 CPMP/EWP/239/95 Rev. 1 Corr.

LEGAL BASIS

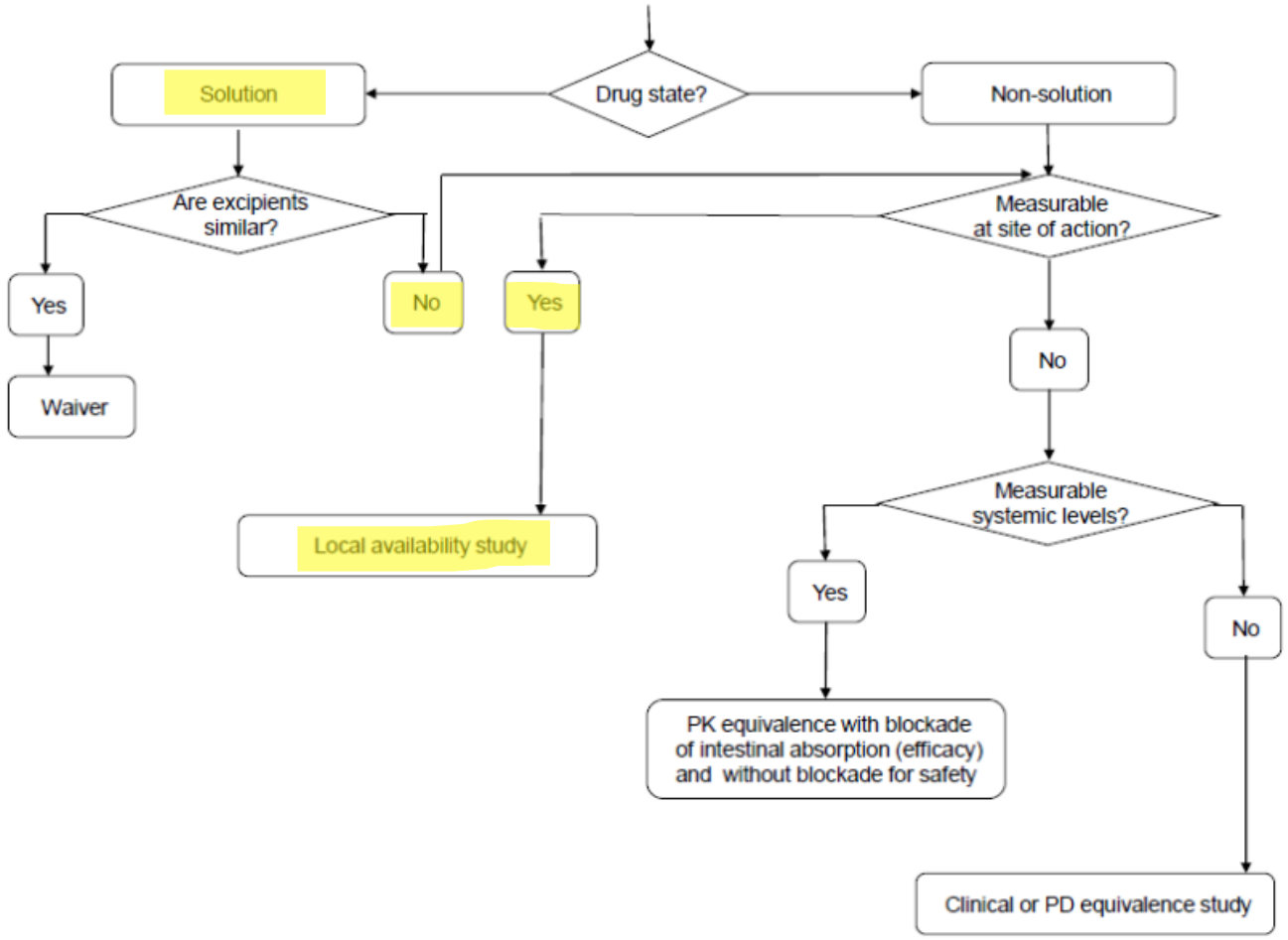
It is justified that the drug is released from the dosage form as a solution due to its high solubility, it is possible to assess indirectly the local availability or the amount released by assessing the amount remaining in the dosage form at selected time points in an in vivo study. The guideline does however not mention to what extent the active substance must be released to ensure a conclusive result. The PKWP is of the opinion that if equivalence is evaluated with this type of study, the lozenges (test and reference) are expected to be completely dissolved during the study time. Given the limited experience at the current time for this type of in vivo study, the PKWP considers that a recovery of >85% is expected, unless otherwise justified.

Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract - Revision 1 CPMP/EWP/239/95 Rev. 1 Corr.

PKWP Q&A 3.10 What is the recommendation on what extent of active ingredient that should be released in a comparative local in vivo availability study, in order to allow a conclusion of comparable local exposure for lozenges? March 2020

LEGAL BASIS

Decision tree for products acting locally in the mouth and/or throat



WHICH APPROACH

Try to avoid complex in vivo study

Try to use in vivo mass loss to assess release of the drug

EXPERIMENT: SET UP

EXPERIMENTS

For both formulations

In vitro:

- Demonstrate that the drug is uniformly spread within the mass
- Demonstrate that mass loss is a good surrogate of release of APIs

In vivo

- Assess accurately mass loss
- Compare time of complete sucking/in vivo dissolution of formulations

IVIVC

- From vivo mass loss extrapolate in vivo release of APIs

IN VITRO DISSOLUTION

Aim assess homogeneity of the lozenges, link of release vs mass loss

Method:

- 15 lozenges per experiment one for each time from 0-15 min
- Vessel filled with a known volume of media specific for each API, stirred at a constant rate => 15 vessels per experiment one by time point
- Asses mass loss of the lozenge and concentration in the media at each time.

IN VIVO STUDY

Standard Phase I Healthy Volunteers 18 years of age & above

Outcome in mass loss over time between lozenges

One measure every 30 second

Standardized procedure to assess it

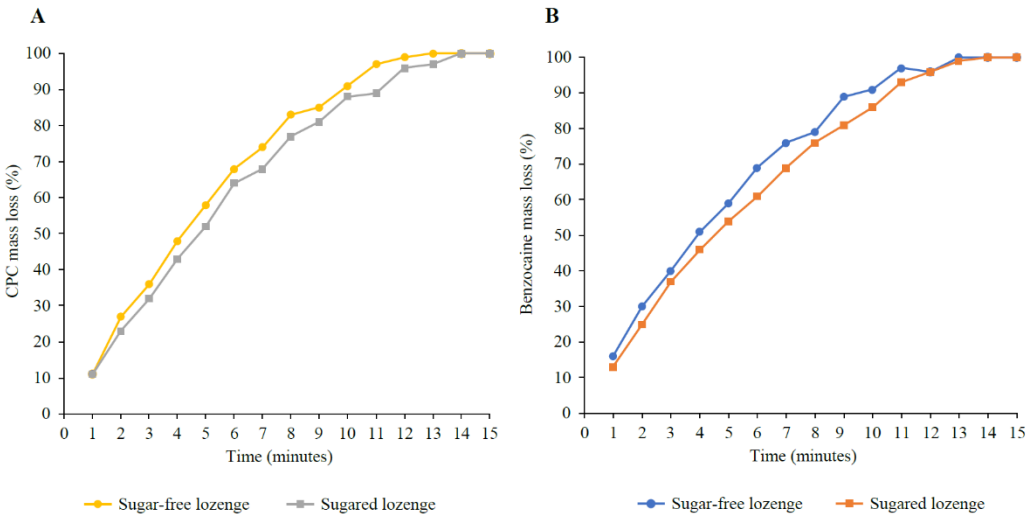
TESTS IN VIVO FINAL ASSESMENT: MASS LOSS

Comparison of in vivo profiles of mass loss (as a surrogate of drug release) and all subsequent parameters if needed, for example:

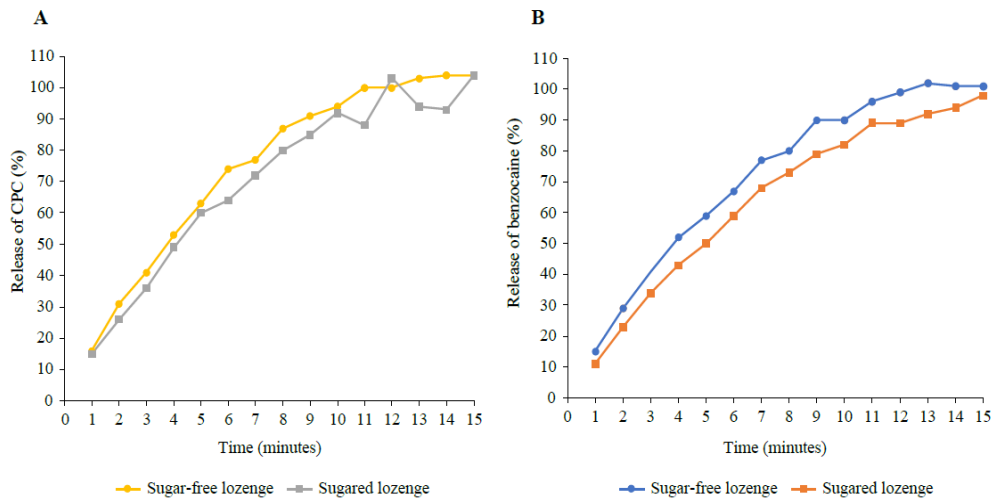
- Time to Complete 85% Mass Loss Kaplan–Meier curves
- Dissolution efficiency (DE) = Mass loss efficiency
- F2 or equivalent on mass loss

EXPERIMENT: RESULTS

IN VITRO RESULTS



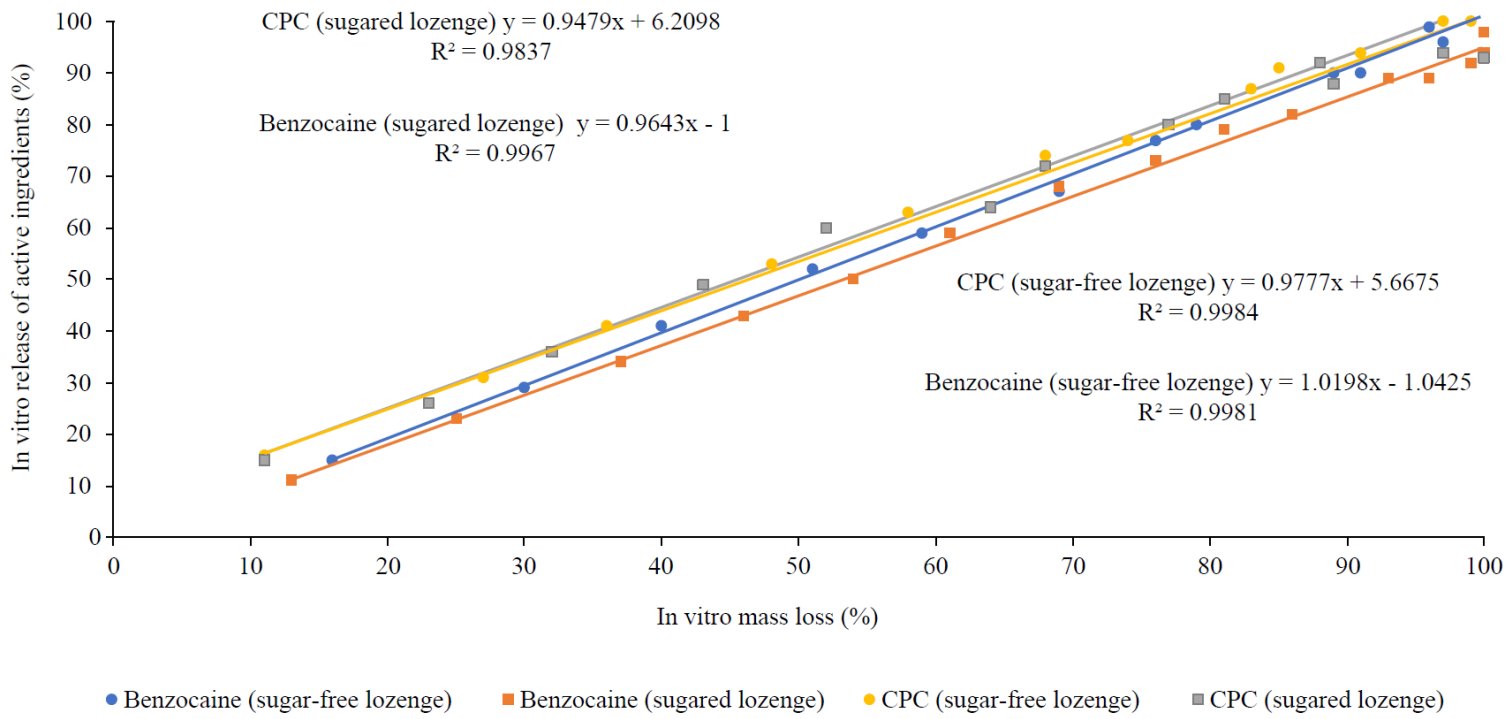
In vitro mass loss of (A) CPC and (B) benzocaine in vitro release experiments from sugar-free and sugared



In vitro release of (A) CPC and (B)

NB: Media specific for each API

IN VITRO MASS LOSS VS RELEASE



Correlation between in vitro mass loss and release of active ingredients from sugar-free and sugared CPC/benzocaine (1.4 mg/10 mg) lozenges

Overall all mass and APIs have a similar relationship for both formulations

⇒ From mass loss API release could be estimated

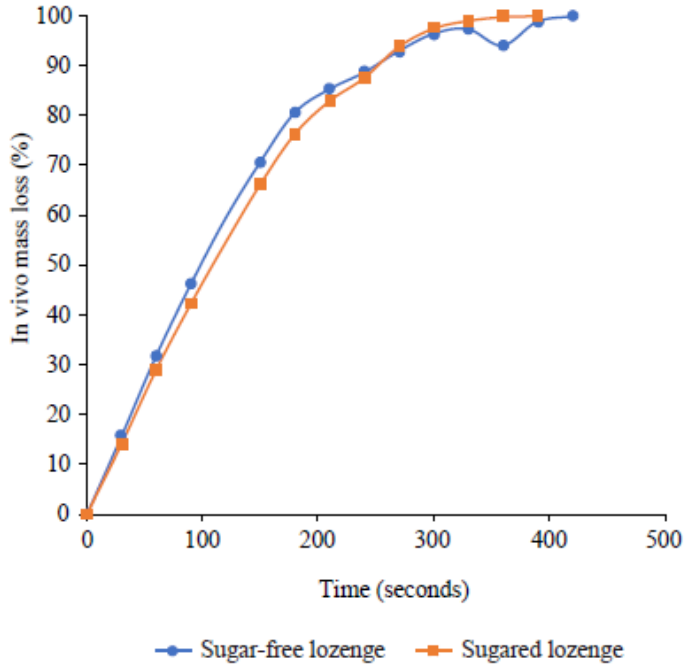
⇒ APIs are uniformly dispersed in the lozenge

IN VIVO STUDY

Standard Phase I Healthy Volunteers 18 years of age & above

Outcome in mass loss over time between lozenges

Standardized procedure to assess it

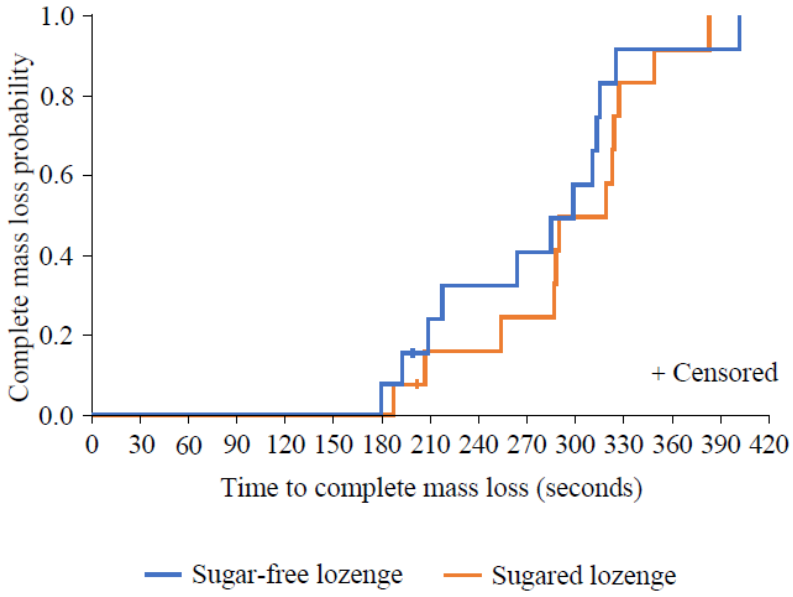


Mean percentage mass loss of sugar-free and sugared CPC/benzocaine (1.4 mg/10 mg) lozenges

IN VIVO STUDY

Outcome in mass loss over time between lozenges

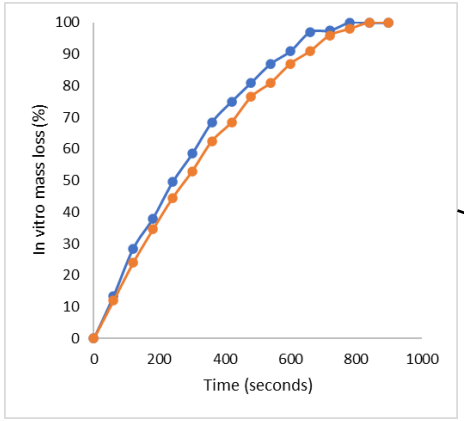
Kaplan-Meier curves for ‘Time to Complete Dissolution’ for sugar-free and sugared CPC/benzocaine

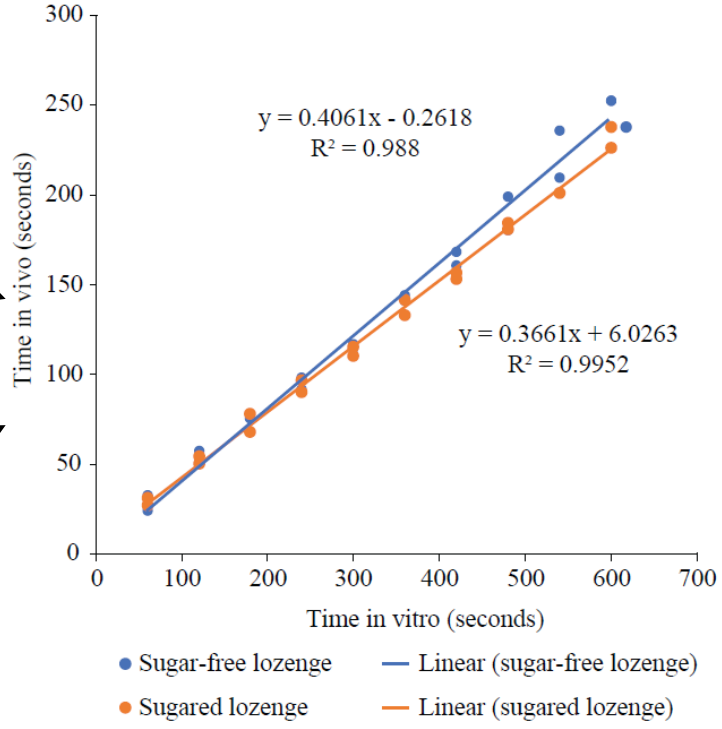


Mass losses in vitro and in vivo have difference in rate: a time scaling is needed

In vitro

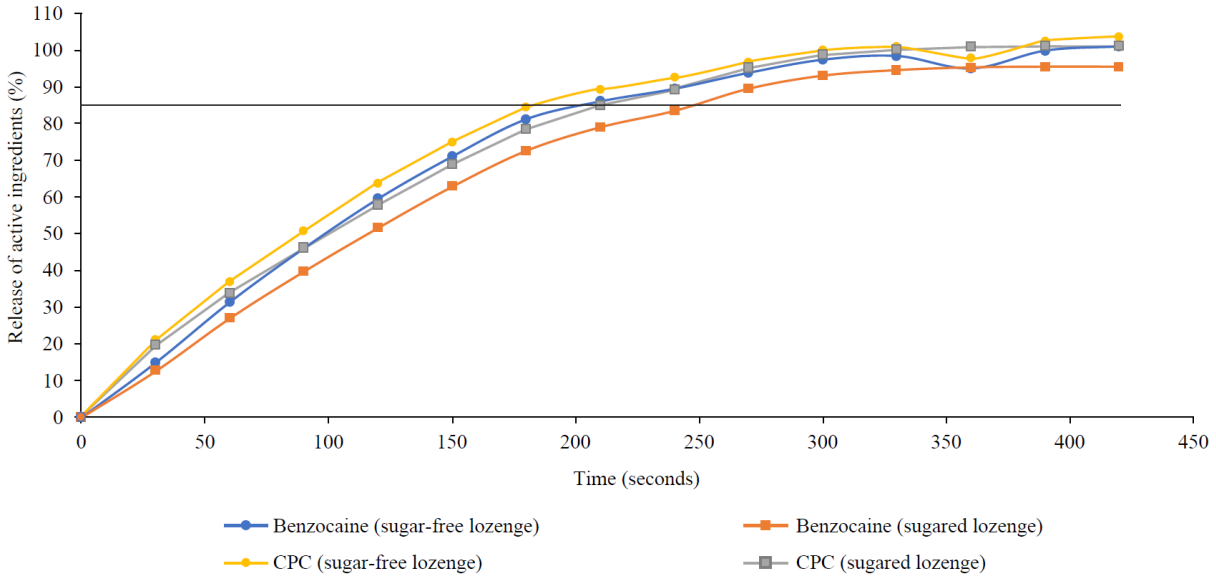
In vivo





Time scaling between mass loss in vitro and in vivo from sugar-free and sugared lozenges

USE OF IVIVC TO PREDICT IN VIVO RELEASE



In vivo release of CPC and benzocaine from sugar-free and sugared CPC/benzocaine (1.4 mg/10 mg) lozenges mean of all individuals

Time to have 85% release

F2 IN VIVO METRICS FOR MASS LOSS

The mean difference was 3.2% (up to first point >85%)

Initial f2 of 68.83%

Boorstrapped: 51.92–95.98,

=> mass loss profiles of the sugar-free and sugared lozenge are equivalent

OTHER METRICS ON MASS LOSS

Median time for complete mass loss299 vs 319 second

Mass loss efficiency 58.64 vs 58.27

All parameters are within a +/-10% limit

METRICS ON IN VIVO RELEASE OF DRUGS ….

The release profiles of both benzocaine and CPC were similar in the oropharyngeal cavity for the sugar-free and sugared lozenges, with a mean absolute difference <10%

The sugar-free and sugared formulations released more than 85% of the active ingredients in 186 and 209 seconds in vivo, respectively

OUTCOME AND CONCLUSION

IN VITRO

Simple tool to evaluate release of the drugs

Confirm homogeneous dispersion of APIs in the mass: lozenge is a « solution »

Confirm that mass loss if a good surrogate of release

Give a first comparison between formulation

Problem at the end of dissolution remaining mass of lozenge are fragile

IN VIVO

Mass loss is a simple tool to evaluate release of the drugs

Avoid swabbing

However increased variability compared to in vitro

Problem at the end of in vivo experiment remaining mass of lozenge are fragile=85% better than complete mass loss

What is the best parameter to compare results?

QUESTION OF LIMITS

Limits

- In vitro limits are set up to ± 10%
- In vivo limits are of ± 20% (of 0.8000-1.2500 after Ln transformation)

Example F2

- In vitro a 10% difference leads to F2=50%
- In vivo F2=50 is that normal ? Using a 20% difference leads to F2=35%

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AKNOWLEDGMENT AND DIRECT REFERENCE TO THIS PRESENTATION

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CARDOT JM, SAVANIA N, TARGETT D, FREEMAN B, GRAY H, STAHL T, KÄSTNER U, KULASEKARAN A.
Validated correlation of in vitro and healthy subjects mass loss and drug release of sugared and sugar free cetylpyridinium chloride (CPC) and benzocaine (1.4 mg/10 mg) lozenges versus in vitro mass loss and corresponding drug release as a surrogate for local bioequivalence
J of Drug Del Sci and Tech 2022 Sept https://doi.org/10.1016/j.jddst.2022.103822

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THANK YOU

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