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# Development of an In-Vitro Chewing Method for Determining Opioid Availability Following Chewing of Solid Oral Extended-Release Opioids


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## PURPOSE

Chewing extended-release (ER) opioid tablets prior to ingestion is one of several methods used by drug abusers to achieve the desired rapid "high" (euphoria) by disabling the extended release mechanism in these types of tablets. The development of abuse deterrent formulations (ADFs) with tamper resistant properties provides an approach to minimize the risk of misusing opioids via this route of abuse.

Currently, no *in-vivo* predictive method exists to assess, how easily the abuse deterrent properties of a formulation can be compromised via chewing. Therefore, the goal of this study is to develop an *in-vitro* chewing method, which can predict *in-vivo* opioid availability following chewing of solid oral opioids.

## OBJECTIVE

The work presented here describes the development and evaluation of an *in-vitro* chewing method for Hysingla, an approved ER opioid that was recognized by FDA as having properties that are expected to deter misuse and abuse via chewing. A commercial chewing apparatus that allowed for the simultaneous determination of drug release while the formulation was mechanically masticated was used for developing a simulated chewing method. To predict the effect of chewing on drug release following chewing and subsequent ingestion, the chewing method was used in combination with a USP dissolution test.

## METHODS

Test formulation: Hysingla (hydrocodone bitartrate) 60 mg ER tablets

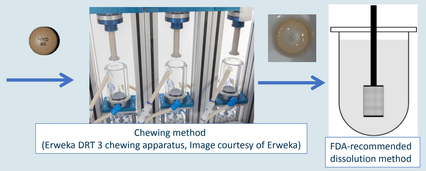
### Simulated chewing experiments

The tablet was placed between two chewing surfaces (jaws). The chewing process consists of up and down strokes of the lower jaw in combination with a shearing (twisting) movement of the upper jaw.

| Test conditions: | |
|---|---|
| Temperature: | 37±0.5°C |
| **Chewing rate (strokes/min):** | **Variable** |
| **Twisting angle (degrees):** | **Variable** |
| **Gap between the jaws (mm):** | **Variable** |
| Test medium: | Artificial saliva pH 6.8 |
| Media Volume: | 40 mL |
| Pre-warming time: | 10 min |
| Force per chewing surface: | ≈ 400 N |

*→ To investigate the effect of variable instrument parameters on the rate of drug release (gap between the jaws, chewing frequency and twisting angle)*

### Simulated chewing experiments followed by dissolution testing




*→ To investigate the effect of chewing time on drug release during simulated chewing experiments followed by dissolution testing*

(Basket, 100 rpm, 900 mL SGF pH 1.2)

## RESULTS

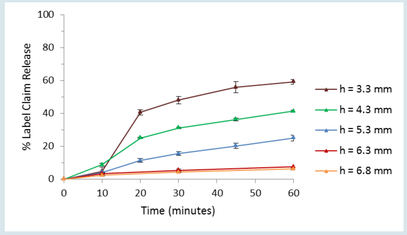



**Figure 1.** Impact of gap size (h) on % Label Claim release during simulated chewing experiments (40 mL artificial saliva, 40 strokes/min, 20 degrees).

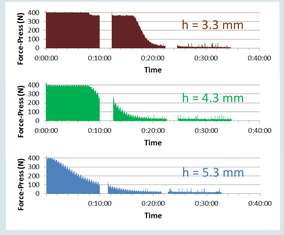



**Figure 2.** Force applied to the tablets during the press movement of the lower jaw during the first three 10 min chewing intervals (bracketed by sampling periods) for three different gap sizes (40 mL artificial saliva, 40 strokes/min, 20 degrees).

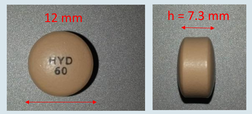



**Figure 3.** Images of intact Hysingla 60 mg ER tablet

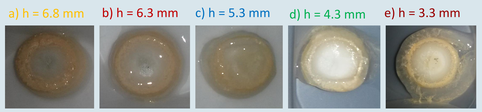



**Figure 4.** Images of tablet residues after 60 min of chewing with different settings for the size of the gap between the upper and lower jaw.

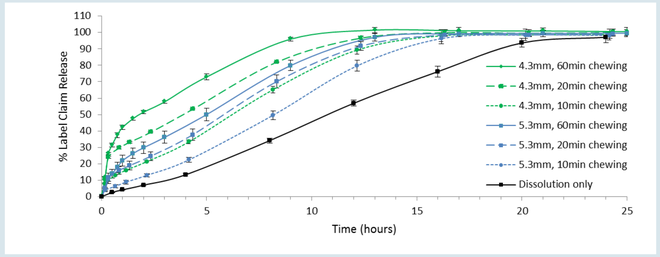



**Figure 5.** Cumulative % Label Claim Release during simulated chewing experiments with different chewing times (10, 20 and 60 min) for a gap size of 4.3 and 5.3 mm followed by 24 h of USP dissolution testing using the FDA recommended dissolution method. For comparison a dissolution profile of intact tablets is plotted in the same graph.

Drug release during the simulated chewing study was clearly affected by the size of the gap between upper and lower jaw (Fig. 1), whereas chewing frequency and twisting angle had a minor effect (data not shown here). After 60 min of simulated chewing, 59.2, 41.3, 25.0 and 7.6% of the labeled dose had been released into the medium in experiments with a gap size of 3.3, 4.3, 5.3 and 6.3 mm, respectively.

- Continuous force monitoring indicated that effective mastication, followed by a reduction in tablet height, took place during the first 10-20 minutes (Fig. 2). For all of the experimental conditions studied, the applied force reached baseline values close to zero within the first 20 min. Furthermore, a burst release was evident in the drug release profiles after 20 min of chewing, whereby the magnitude of the burst decreased with gap size (Fig. 1).
- Figure 5 shows the drug release profile of tablets that were first exposed to a simulated chewing cycle and subsequently transferred into a dissolution apparatus for dissolution testing. While the amount of drug released during the simulated chewing cycle was clearly affected by the gap size and chewing time, the drug remaining in the formulation after simulated chewing was released with a similar rate during the dissolution test for most of the conditions investigated. Compared to intact tablets the tablet residues released the drug remaining in the formulation with a slightly faster rate but the extended release properties were maintained.

## CONCLUSIONS

- The degree of mastication during simulated chewing and thus the course of the overall drug release profile (simulated chewing and dissolution) were affected by the size of the gap between the upper and lower jaw which determines the force that was exerted on the tablet over time. In addition to the gap size, the course of the drug release profile was sensitive to the chewing time.
- Identification of *in-vivo* predictive test parameters for the chewing method will be guided by pharmacokinetic modeling and simulation work using in house PK data for chewed and ingested Hysingla.
- The ability of the chewing method to adequately predict the *in-vivo* behavior of additional opioid formulations with properties that are intended to deter misuse and abuse via chewing will be explored in future studies. Based on experiences with different drug products the method may be further refined and optimized.

## FUNDING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