In Vitro Differentiation of Two FDA-Approved Abuse-Deterrent Opioids' Resistance to Oral Mastication

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Background and Purpose

Abusers often physically manipulate or 'tamper' with prescription opioids for oral and non-oral routes of administration.[1] Oral mastication, or chewing, is commonly employed for both immediate-release and extended-release to speed release of the active pharmaceutical ingredient (API). Many abuse-deterrent formulations (ADFs) are designed to be physically hard and resist physical manipulation by tools; however, few products have earned a label claim for resistance to oral abuse by mastication. Early development studies completed by DRUGSCAN explored the complex set of experimental conditions that are required for in vitro simulated mastication studies (e.g., bite force, torsion degree, saliva, temperature, time). In extension of the exploratory investigation, this study further optimized the method's compression, force and time parameters and included an additional ADF comparator with claims of resistance to oral mastication. Here, we discuss and provide the results of a mastication study that evaluated one ADF with oral mastication claims (ADF_1) relative to another ADF with physical, chemical, and injection claims but, without oral mastication claims (ADF_2). A non–abuse-deterrent commercial (non-ADF) was included as a control.

Materials and Methods

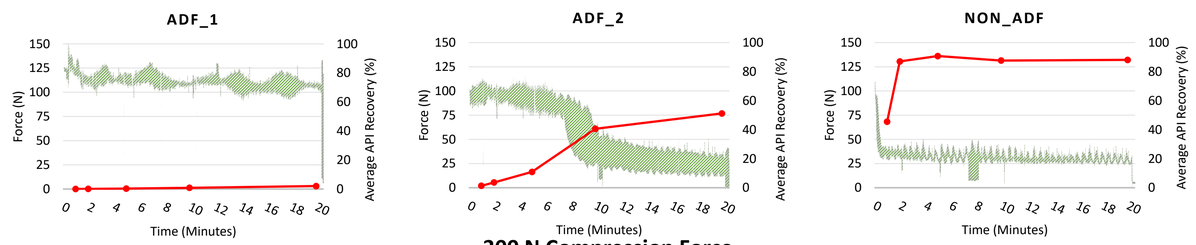
This study was designed to simulate the several conditions encountered during in vivo mastication. Utilizing the DRT manufactured by ERWEKA GmBH (Heusenstamm, Germany) and simulated saliva manufactured by Pickering Labs (Mountain View, CA), temperature, compression force and distance, torsion degree, mastication frequency and duration can be tightly controlled to optimize these studies.[3] The media (20 mL of simulated saliva) and mastication jaws were equilibrated to human body temperature (37°C) before the addition of any pharmaceutical formulation and held at a constant temperature for the 20-minute mastication study. Human bite forces have been shown to vary greatly even within closely related populations.[2] Three representative maximum forces (Newtons) of approximately 110 N, 300 N, and 550 N were examined with compression gap distance representative of 80-85% compression of the formulation's starting thickness. A characteristic torsional degree of 20° and mastication frequency of approximately 40 strokes/min (1.57 Hz) were used for all experiments.[4,5,6] Aliquots of the simulated saliva were removed at 1, 2, 5, 10 and 20 minutes to measure the release of API in solution. Force and torque data was electronically recorded and was plotted to allow investigation of force and torque changes over the course of the study. Experiments were conducted in triplicate.

Results

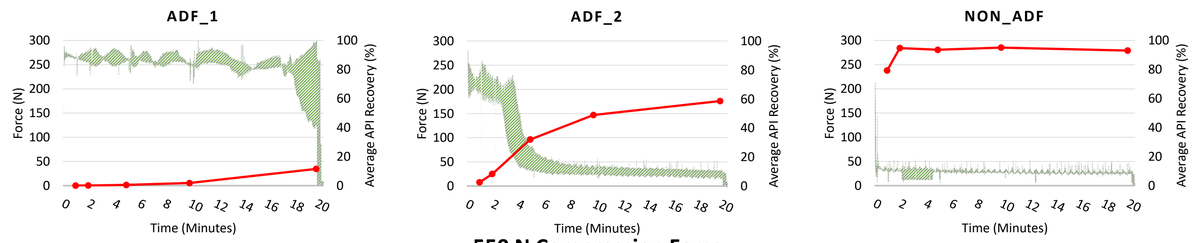
- The non-ADF product was rapidly deformed within the first minute of mastication and all API from the labeled dose was released within 2 minutes at all tested forces
- At all API measurement time points ADF_1 (with oral mastication claim) and ADF_2 (without oral mastication claim) showed a significant difference (student's t-test) as compared to the non-ADF control at all compression forces (P<0.01)
- Tested at 300 N, ADF_1 began to deform after approximately 19 minutes and only 12% API was released
- Tested at 550 N, ADF_1 began to deform after approximately 11 minutes and produced a slightly higher average API recovery of 33%.
- At all tested time points and compression forces, the API recovery from ADF_1 (with oral mastication claim) was significantly lower than the API recovery from ADF_2 (without oral mastication claim) (P<0.01)

	Drug Product Deformation Observed (minutes)			Avg. % API Recovery at Deformation		
Test Article	110 N	300 N	550 N	110 N	300 N	550 N
Non-ADF	0.5	0.1	0.1	88	95	97
ADF_1	20	19	11	2	12	15
ADF_2	8	3	1	41	32	44

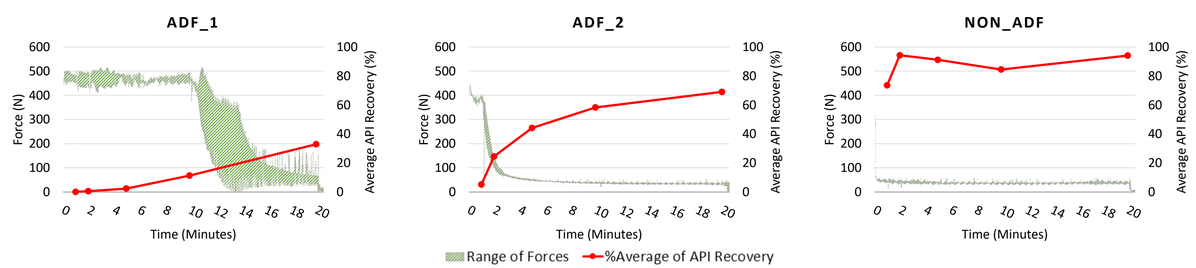
110 N Compression Force



300 N Compression Force



550 N Compression Force



Conclusions

- This study differentiated mastication resistance of commercially available ADF_1 (claim for oral mastication resistance) compared to ADF_2 (no claim for oral mastication) and the control.
- These data show ADF_1 is superior to ADF_2 even when subjected to very high bite forces for up to 20 minutes.
- The decrease in force and the increase in API recovery indicates the deformation of the drug product. Less force is required to compress the drug product to the same thickness over time.
- This study suggests that products with resistance to physical manipulation (as with ADF_2) and other routes do not de facto deter abuse via mastication.
- An important next step will be to evaluate the in vitro/in vivo correlation via an oral drug liking study and potentially develop an in vitro modeling approach.
- In future studies, variations of the mastication program should be explored where low force mastication (100 – 200 N) is punctuated by brief intervals of high force (550 N). This may simulate the ability of a human to apply strong bite forces but, for only short periods of time.

References

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