# Caffeine Anhydrous Taste Masking by Hot Melt Extrusion

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## INTRODUCTION

The taste masking of bitter APIs is a major challenge especially for pediatric formulations. Various reported approaches include, fluidized-bed coating, complexing agents, Pro-drug formation, etc. However, there is an enormous need for more robust, cost effective and easy to scale-up taste masking technologies. Hot Melt Extrusion (HME) is a continuous, one step process which also been introduced for taste masking purposes of bitter APIs by involving the use of taste masking polymers that create solid dispersions to prevent bitter drugs from coming in contact with the patient's taste buds.

**OBJECTIVES:** The main objective of this project was to investigate the potential of KLEPTOSE® Linecaps DE17 (a pea maltodextrin with a DE range of 15 – 20) in masking the bitter taste of Caffeine Anhydrous (CA) by Hot Melt Extrusion (HME) and to evaluate its efficiency in a taste panel.

## MATERIALS & METHODS

- Thermogravimetric studies were performed on the KLEPTOSE® Linecaps DE17 (KLD) and xylitol to determine thermal stability during extrusion. The physical characterization of pure CA, KLD, xylitol and extruded formulations was performed by differential scanning calorimetry (DSC).
- In order to increase KLD extrudability, Xylitol was used as plasticizer at 15% w/w. CA at 15% w/w load were pre-mixed with KLD and xylitol using a V-shell blender and further extruded using co-rotating twin screw extruder (16 mm Prism Euro Lab, ThermoFisher Scientific) at screw speeds of 100 rpm at temperature 150/155°C.
- Milled extrudates were studied for *in vitro* dissolution release in simulated saliva fluid (pH 6.8) *using USP* Type-I apparatus at 37 ± 0.5 °C and 75 rpm. Samples were analyzed using a Waters HPLC-UV system (Waters Corp).
- Human panel palatability studies were performed in nine healthy human volunteers from whom informed consent was obtained previously (Ethics committee approval # VIPS/2013/12). The subjects were asked to taste CA in a physical mixture (PM), HME granules after milling (Sieve #40 pass and #50 retains) and HME granules after milling (250 mg) plus 50 mg of Linecaps DE17 equivalent to 40 mg of CA by holding the formulation on tongue for 30-40 sec and then spat out. The bitterness was recorded immediately on a scale of 0-5 based on modified hedonic scale, where 0 indicate none and 5 indicate strong bitterness.

## RESULTS & DISCUSSION

Dissolution studies of HME extrudates exhibited <5% release of the API in simulated saliva fluid, whereas physical mixture showed ~15% release at the end of 5 min.

**Figure 1.** DSC Thermograms of Xylitol, Caffeine Anhydrous and Extrudates.

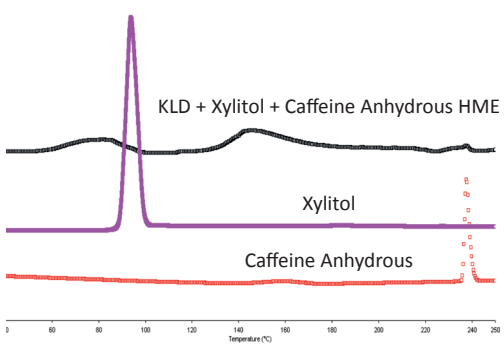
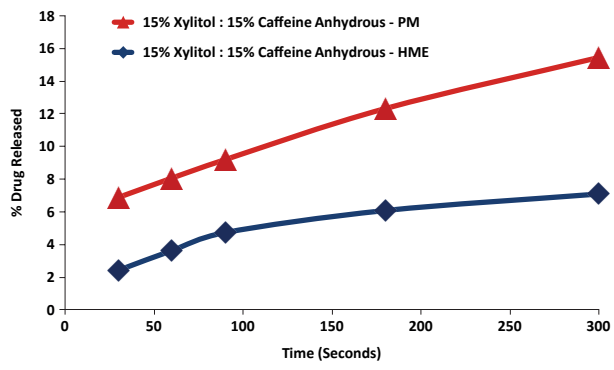



**Figure 2.** Dissolution profiles of HME formulations and physical mixture (PM) containing 15% w/w drug load with 15% w/w xylitol as plasticizer.



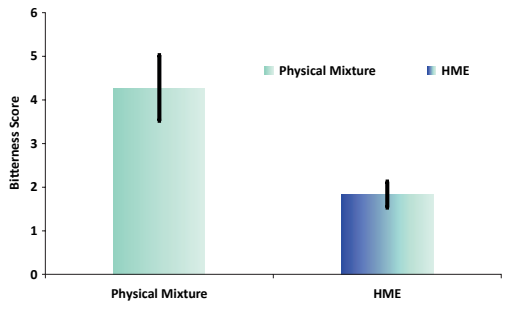

### Human Panel Studies of Taste Perception (Gustatory Response Studies)

- *Human subjects:* A total of 9 subjects belonging to either sex with significantly low threshold. They were asked to stay away from coffee/tea and other beverages for 12 hours. Only water was allowed to drink. They were asked not to eat chocolates or candies for over 6 hours.
- *Study site:* Institute for Drug Delivery and Biomedical Research, Bangalore, India.
- The subjects were asked to wash their mouth with ambient water prior to testing.
- The surface temperature of the tongue was recorded using an IR thermometer.

**Table 1.** Taste scores given by each individual to physical mixture and HME formulation.

| Subject Inclusion Criteria | Amount (mg) of API in 2ml water | Volunteers | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Healthy human subjects of age 18-42. | | I | II | III | IV | V | VI | VII | VIII | IX | | |
| | Water (no API) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| | 0.5 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | Threshold of the subjects is in this range (Less than 40 mg) | |
| | 1 | 2 | 0 | 1 | | 1 | 4 | 3 | 1 | 2 | | |
| | 5 | 3 | 1 | 4 | 1 | 3 | 5 | 4 | 4 | 3 | | |
| | 10 | 4 | 2 | 4.5 | 5 | 5 | | 5 | 5 | 4 | | |
| | 40 | 5 | 4 | 5 | | | | | | 5 | API equal to that in test formulation (40 mg) | |
| Subject Exclusion Criteria | Product testing (250 mg powder/granules) equivalent to 40 mg of CA | | | | | | | | | | Average | Standard Deviation |
| Subjects suffering from fever, smokers, mouth boils and wounds | Physical mixture | 5 | 3.5 | 4 | 5 | 3 | 5 | 4 | 4 | 5 | 4.28 | 0.75 |
| | HME granules | 1 | 2 | 2 | 3 | 2 | 0.5 | 2.5 | 3 | 0.5 | 1.83 | 0.97 |
| Oral cavity temperature 36 ± 5 | HME granules +Linecaps DE17 (50mg) | 1 | 1 | 1 | 1 | 1 | 0.5 | 0.5 | 1 | 0 | 0.78 | 0.36 |

**Figure 3.** Average scores given by volunteers for caffeine anhydrous drug in physical mixture and HME formulation.




- The results from the human panel studies demonstrated strong bitter taste in case of PM with the average score of 4.27±0.75, whereas the HME formulation resulted in 1.83±0.96.
- The results from the human panel studies are demonstrating a significant CA taste masking effect due to KLD processed by HME over the physical mixture.

## CONCLUSION

The DSC studies revealed a characteristic melting endotherm of CA at 236-240 °C in the physical mixtures as well as in all extrudates over the period of study, indicating the crystalline nature of the drug. HME of CA at 15% drug load using KLD as a matrix and Xylitol as a plasticizer demonstrated very good extrudability. Lower release of CA (<5%) could suggest the potential use of KLD in development of taste masked formulation by HME for a reconstitutable suspension (in the first 60 sec. of dissolution lower release → the better the taste masking). Results from the human panel studies are suggesting the potential use of KLEPTOSE® Linecaps DE17 in development of taste masked formulation by HME, which may be further formulated and developed as dosage forms for geriatric and pediatric populations.

**REFERENCES**

C Popescu, A Juluri, M B Pimparade, V I Kulkarni, L Zhou, M A Repka, S N Murthy. Griseofulvin Taste Masked by Hot Melt Extrusion for Pediatric and Geriatric Reconstitutable Suspension. San Antonio, AAPS 2013.