The Palatability FDTs Containing LPV/r and Their Ability to be Masked by Sucrose

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Abstract

The purpose of this study was to determine if the bitterness of freeze dried tablets (FDT) containing lopinavir and ritonavir (LPV/r) could be masked by sucrose in order to be less aversive. We matched the bitterness of the four concentrations of FDT containing LPV/r to three concentrations of quinine hydrochloride (Q-HCl) and then combined these chemical stimuli with two concentrations of sucrose in order to examine if the bitterness of FDT could be masked. Rats were exposed to behavioral testing in order to measure if the bitterness of the solution had an effect on licking patterns. As hypothesized, results showed that sucrose at 750 mM effectively masked the bitterness of the Q-HCl stimulus for all solutions. However, the addition of sucrose to FDT containing LPV/r showed no effect on oromotor responses. There were no significant effects of any stimulus on the latency to approach and lick the spout. Matching aversive concentrations of FDT and Q-HCl differed significantly on their ability to be masked by sucrose, therefore we conclude that there is an additional negative hedonic stimulus associated with FDT containing LPV/r beyond its aversive bitter taste that sucrose could not mask.
The Palatability of FDTs containing LPV/r and Their Ability to be Masked by Sucrose

Human immunodeficiency virus (HIV) is a sexually transmitted disease that weakens the immune system. The virus targets T helper cells (t-cells) and prevents them from replicating. T-cells play a crucial role in cell immunity. Overtime, the virus can illuminate so many t-cells that HIV can ultimately develop into a fatal disease known as acquired immune deficiency syndrome (AIDS). HIV is a very serious health issue for countries all over the world. According to the Centers for Disease Control and Prevention (CDC), more than 36.9 million people are currently living with HIV worldwide (CDC, 2016). Since the 2000’s, more than 25.3 million people have died from AIDS worldwide (CDC, 2016). There is not currently a cure for HIV or AIDS, but there are preventative measures and treatments that can be utilized in order to decrease the spread of the virus. One successful treatment method for HIV is known as antiretroviral therapy, which is the combination of antiretroviral medication drugs to maximize the suppression of HIV (WHO, 2013). The combination of lopinavir and ritonavir (LPV/r) is an effective method for treating HIV. LPV/r works to decrease the levels of HIV in the blood, allowing t-cells to replicate which strengthens the immune system.

The World Health Organization (WHO) recommended either abacavir or zidovudine with lamivudine and LPV/r as a first line antiretroviral therapy for all HIV-infected infants and children between 14 days and three years of age in their 2013 guideline publication on the use of antiretroviral drugs (WHO, 2013). The WHO does note the possible challenges when attempting to administer LPV/r to its intended population. LPV/r 80mg/20mg/ml oral liquid formulation contains 42% ethanol and 15% propylene glycol and thus is very aversive (WHO, 2015). The oral liquid is also not heat stable and requires refrigeration up to the point of administration, which challenges the logistical availability of the drug. Musiime et al. (2014) also noted how...
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pediatric ritonavir as a booster for other protease inhibitors is only available in a large 100mg tablet or highly unpleasant tasting liquid, therefore he says there is an urgent need for highly palatable LPV/r formulations that do not require cold-chain shipping and stowing. The poor palatability of LPV/r oral solution is a significant barrier to medication adherence. Examples of interventions that may improve pediatric adherence and tolerability include: taste bud numbing with ice chips before or after administration, masking the aversive taste with sweet or tangy foods, chocolate syrup, peanut butter, or the pharmacist can flavor the solution before hand (Musiiime, 2014). Alternate pediatric formulations are currently being developed.

The PATH pharmaceutical company has focused some of their research efforts on decreasing LPV/r oral solutions’ dependence on cold-chain transportation and storage. PATH says that keeping products such as the LPV/r at the temperature range of two degrees Celsius to eight degrees Celsius requires a cold chain: “a global distribution network of equipment and procedures for maintaining product quality during transport, storage, and distribution” (PATH, 2016a). In order to optimize product stability, PATH has developed freeze-dried tablet technology. Freeze drying (lyophilization) creates a dried product design by freezing the oral liquid solution and then eradicating the water particles through prevention under vacuum conditions (PATH, 2016b). Freeze drying increases product stability by increasing the temperature threshold while maintaining potency during transportation and storage in countries and communities with restricted dependable power for refrigeration needs. However, when FDT’s are mixed with water for oral administration, there is still the potential for a highly aversive taste associated with the oral drug solution. So while technologies have been developed to optimize product stability, researchers still have to focus their endeavors towards making the FDT’s palatable enough for pediatric patient adherence.
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Taste masking is an essential factor in the development of oral dosage forms containing bitter active pharmaceutical ingredients. Kaushik and Dureja (2014) summarize numerous techniques that have been described in literature that pertain to masking the unpleasant taste of drugs, as well as provide insights into the new and innovative taste masking technologies available. The conventional taste masking approaches that are reviewed include: flavors and sweeteners, film coating, microencapsulation, ion exchange resin complexation, and rheological modification. Flavors and sweeteners are the simplest way to mask an aversive bitter taste (Kaushik & Dureja, 2014). This process involves binary mixture suppression where the sweet taste masks the aversive component of the solution. However, researchers note that this method is not successful for highly aversive and soluble drugs (Kaushik & Dureja, 2014). Film coating involves coating the bitter drug to mask the taste without affecting the release time. However, this method is not perfect and the release of the drug can still be affected. Microencapsulation methods such as coacervation phase separation, spray drying, and fluid bed coating involves applying a thin coating to small bitter drug particles in order to mask the aversive taste (Kaushik & Dureja, 2014). Limitations to the microencapsulation process include low efficiency in encapsulation and organic solvents raise environmental concerns. In ion exchange resin complexation, aversive drugs can be attached to the “oppositely charged resin substrate, forming insoluble adsorbates or resonates through weak ionic bonding” (Kaushik & Dureja, 2014). This method is not intended for low pH drugs and can negatively affect onset of the drug. Cyclodextrin complexation masks the aversive drug by decreasing its oral solubility on ingestion, or it decreases the amount of aversive particles exposed to taste buds (Kaushik & Dureja, 2014). This method is highly dependent on the physicochemical properties of the drug however. The bioavailability, which is the amount of original drug that circulates in the blood to
all parts of the body, of lopinavir was enhanced significantly using cyclodextrin complex tablet formulation (Goyal & Vavia, 2012). Rheological modification increases the viscosity of the aversive liquid, which limits drug interaction with the tongue (Kaushik & Dureja, 2014). This method could prolong the duration of the aversive aftertaste however.

Presented next are the new and innovative ways researchers have been developing taste-masking technologies. Nanohybrid technology involves nano-ordered composite materials, which consist of organic polymers, and inorganic materials (Kaushik & Dureja, 2014). This technology works by retarding the release of the drug long enough to mask the bitter taste. Hot-melt extrusion technology involves mixing and melting the bitter drug, polymer, and other excipients in a melt extruder then forcing the compound through dies with rotating screws to reach the desired drug concentration (Wilson, Williams, Jones, & Andrews, 2012). Kanikanti et al. (2010) developed the extrudates for taste masking of bitter drugs through the melt extrusion process using a small strand diameter to reduce the release of the active ingredient in the oral cavity. Cold solvent-free extrusion utilizes a coating on pellets that inhibits the release of the drug based on temperature and time within that temperature and it was an effective taste-masking technique (Kaushik & Dureja, 2014). In porous microsphere technology the bitter drug was granulated with a porous microsphere component, which loads the drug into the pores of the microsphere leading to its taste masking (Kaushik & Dureja, 2014). Rupturing multiparticulates technology is the creation of microparticulates, which do not rupture in the oral cavity, rather they rupture in the stomach to mask the bitter taste of the drug without interfering with its release (Kaushik & Dureja, 2014). Off taste masking uses agents such as methylsulfonylmethane to block the off taste presented by some sweeteners (Kaushik & Dureja, 2014). Newer cyclodextrin compositions are also being created. Friesen et al. (2008) developed a formulation comprising
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the bitter drug in a dissolution-retarded form and/or cyclodextrin in a dissolution-enhanced form that resulted in the retardation of the bitter drug in the oral cavity, which led to taste masking.

The use of lipid-based particle delivery system offers the ability to control the size of the final particle by controlling the number of nano-lipidic particles used to assemble the finished particle (Kaushik & Dureja, 2014). Nano-lipidic particles have shown great potential in bitter drug taste masking. Film coatings with improved disintegration provide a more rapid delivery and faster onset of the drug (Kaushik & Dureja, 2014). Finally, Kashid et al. (2010) developed a taste masking technique using absorption. Kashid et al. (2010) used a technique where the active ingredient was blended with an absorbent to achieve taste masking. This method coupled with the inclusion of a water-soluble polymer strengthened the masking potential even further.

However, our current study utilized a conventional approach by masking bitter quinine hydrochloride (Q-HCl) and highly aversive FDT’s containing LPV/r using the sweetener sucrose. A study conducted by Mennella, Reed, Mathew, Roberts, and Mansfield (2015), revealed that sucrose suppressed the bitterness of a range of moderately bitter stimuli in children. Sucrose is clearly an effective masker of bitter taste. However, adding sucrose to oral pediatric medications comes with oral health concerns (Mennella et al., 2015). Medical and dental professionals advocate for the use of nonnutritive substitutes in children’s oral medications to combat these oral health concerns. Also, excess sugar intake poses several other health concerns such as pediatric diabetes (Li, Servant, & Tachdjian, 2011). Nonnutritive substances such as artificial sweeteners have been used to reduce the sugar content in oral pediatric medications, however as we stated earlier Kaushik and Dureja (2014) revealed several artificial sweeteners produce off-taste that are highly bitter or taste like metallic, which results in non-adherence to
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oral medications. Also stated previously, sweeteners have not been successful in taste masking of highly aversive and water-soluble drugs (Kaushik & Dureja, 2014).

The purpose of this study was to determine if the bitterness of Freeze Dried Tablets (FDT) containing LPV/r could be masked in order to be less aversive. The theory is that since the LPV/r is bitter, the rats perceive it as aversive and therefore do not want to consume it. We want to see if we can add a masking stimulus that will make it more appetitive and therefore yield higher standard lick ratios. We hypothesized that adding sucrose to the LPV/r will mask the bitter taste, therefore making it less aversive.

Method

Subjects

Thirteen naïve, male Sprague-Dawley rats were obtained from Charles River Laboratory in Raleigh, NC in order to be used in this study. The rats were single housed in a climate controlled room with a 12:12-h light:dark cycle (11:30 – 23:30). The rats were allowed free access to food, but were restricted to water throughout the day, only gaining access for fifteen minutes after testing had concluded for that day. Testing on the rats began at noon everyday throughout the course of the experiment. The Institutional Animal Care and Use Committee of Wofford College (IACUC) approved all procedures of this study.

Chemical Stimuli

Each chemical stimuli was prepared each day prior to testing. Four concentrations of freeze dried tablets containing LPV/r were tested in addition to three quinine hydrochloride (Q-HCl) concentrations as well as two sucrose concentrations that acted as masks. FDT 1:30 was the lowest concentration of the four and consisted of one LPV/r tablet dissolved in thirty ml of water and was considered to be a body weight adjusted dose. Listed in increasing concentration, FDT
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1:3 consisted of one tablet in three ml of water, FDT 1:2 consisted of one tablet in two ml of water, and FDT 1:1 consisted of one tablet in one ml of water. Three concentrations of Q-HCl were tested (1.5 mM, 2.0 mM, and 2.5 mM). Two different concentrations of sucrose (250 mM and 750 mM) were used as masking agents for both the FDT and the Q-HCl.

Behavioral Testing

The rats were placed in brief access test chambers (MS-160, Dilog Instruments) that isolated the orosensory influences on rats licking by providing controlled access to tastants. The rats were placed in the chambers one at a time and exposed to thirty trials of the chemical stimuli mentioned above, as well as intermittent water trials presented during each testing session. Licking to water trials were used to normalize stimulus licks to account for individual differences in lick rates and motivation. The isolation of the chambers minimizes olfactory and post ingestive cues for licking behavior by only presenting one tastant at a time for a brief duration. At the beginning of each trial the shutter of the rig would open, at which point the bottle spout would then be accessible to the rat. The spout allowing access to the tastant would remain available for 30 seconds after initial lick and then the shutter would close, blocking access to the tastant. Rats had a 30 second opportunity to approach the spout and initiate the first lick, after 30 seconds a new trial or a re-try trial would begin. Initiating the first lick within 10 seconds was a good indication that the rat was motivated to approach and sample the stimuli. The chambers allowed for licking to multiple concentrations to be analyzed in each testing session. The total number of licks, latency until first lick, and averaged interlick interval, were recorded for each testing session.

Data Analysis
The total number of licks, latency, and average interlick interval recorded for each stimulus, was then converted into a Standardized Lick Ratio (SLR) that accounted for individual differences in lick rates independent of the motivational state the rat was in during testing (Dotson and Spector 2004; Glendinning et al., 2002). Maximum potential lick rate was calculated by dividing the duration of the stimulus trial by the average interlick interval (>50ms and <200ms) during the water training sessions. By dividing the average number of licks for each subject’s maximum potential lick rate, the Standardized Lick Ratio was created. Therefore we are left with a number that represents the greatest number of licks that a single rat could lick in a 30 s trial. Standardized Lick Ratio becomes a ratio where 1.0 represents max number of licks possible, 0.5 represents half maximum licks and 0.0 represents no licks by dividing the average licks per stimulus by maximum potential licks. Latency until first lick represents a measurement of stimulus control and ability for non-oral cues, such as olfaction, to guide licking behavior. If the rat detects the stimulus through visual or olfactory cues before licking the stimulus, the time that the rat will take to approach the spout and initiate the first lick will be longer.

**Results**

There was a significant main effect of FDT concentration on standard lick ratios $[F(4,48) = 1076.055, p < .001]$. However, there was no significant difference in the licking ratios of water and the lowest concentration of FDT diluted in 30ml of water (FDT 1:30). As shown in Figure 1, the lick ratios for FDT 1:30 and water were significantly ($p < .01$) different from the other three solutions, FDT 1:3, FDT 1:2, and FDT 1:1. The FDT concentration of 1:1 had significantly ($p < .01$) lower lick responses than any of the other concentrations.

There was a main effect of concentration $[F(2,34) = 12.356, p < .001]$ when comparing just the three highest FDT concentrations. Pairwise comparisons show that the FDT 1:3 had
higher lick ratios than FDT 1:2 (p = .020) and FDT 1:1 had lower lick ratios than both FDT 1:2 (p = .004) and FDT 1:3 (p = .020). As seen in Figure 2, there was a significant (p < .05) decrease in licking from the FDT concentration 1:3 to 1:2, and also from the FDT concentration 1:2 to 1:1. Figure 2 also shows that there was a significant (p < .01) difference in the decrease of lick ratios of FDT 1:1 in comparison to all concentrations. These results indicate that the solutions with the stronger FDT concentrations were more aversive than the solutions with lower FDT concentrations, resembling water. The higher FDT concentration makes the solution more aversive, therefore lowering the number of overall lick responses.

As shown in Figure 3, there was a significant main effect of quinine hydrochloride (Q-HCl) concentrations \(F(3,51) = 68.061, p < .001\). Pairwise comparisons show that there was no significant difference in the three Q-HCl concentrations on licking. The figure shows that there was a significant (p < .01) decrease in the lick ratios for all three Q-HCl concentrations in comparison to water. This shows that all of the Q-HCl concentrations were equally as aversive.

There were no significant differences in the low, medium, and high FDT and Q-HCl concentrations. This means that there was no significant difference in the aversiveness of the Q-HCl concentrations and the FDT concentrations. Figure 4 shows that the three Q-HCl concentrations are equally as aversive as the three FDT concentrations. This means that Q-HCl is an effective replacement for the FDT when measuring the lick ratios when exposed to a certain level of bitterness.

There was a significant main effect of FDT concentration \(F(2,24) = 6.750, p = .005\), however there was no main effect for the sucrose mask. There was also no significant interaction between FDT and the sucrose mask. As shown in Figure 5, these results show that licking
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decreased as it went from the weaker concentrations of FDT to the strongest concentration of
FDT regardless of the sucrose mask.

There was a significant main effect of the Q-HCl concentration \[ F(2,34) = 3.890, p = .030 \] as well as a main effect for the sucrose mask \[ F(2,34) = 54.221, p < .001 \], but no significant interaction between the Q-HCl concentration and sucrose mask. As shown in
Figure 6, there was a significant increase in licking when the sucrose mask was added to
the Q-HCl, compared to when Q-HCl was presented alone \( p < .01 \). There was also a
significant increase in licking the Q-HCl when the 250 mM sucrose mask was present \( p < .05 \).

There was a significant main effect of concentration for both FDT 1:30 and water
\[ F(4,48) = 8.703, p < .001 \]. As shown in Figure 7, typical small interlick intervals associated
crable stimuli compared to FDT 1:3, 1:2 were observed and 1:1 showed an increased interlick
interval associated with aversive taste (all pairwise comparisons, \( p < .01 \)).

Figure 8 reveals that there was a significant main effect of Q-HCl concentration \[ F(3,51)
= 4.600, p = .006 \] in comparison to water. Q-HCl concentrations were more averse than water
therefore there were higher interlick intervals. As you can see in Figure 8, the Q-HCl
concentrations of 1.5 and 2.0 had a highly significant increased interlick interval when compared
to water, \( p < .01 \). Q-HCl concentration of 2.5 also had a significant increased interlick interval
compared to water, \( p < .05 \).

As you can see in Figure 9, there was no significant difference between the interlick
interval of FDT concentrations and Q-HCl concentrations. This indicated that the averseness
between the two concentrations were comparable.
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In Figure 10, when we added 250 mM and 750 mM of sucrose to each concentration of FDT in order to mask the averse taste and decrease the interlick interval we saw no significant main effects. Sucrose did not mask the aversive FDT.

However in Figure 11, when we added the same sucrose concentrations to each Q-HCl concentration there was a significant main effect of the masking stimulus \( F(2,34) = 11.094, p < .001 \). As you can see in Figure 11, 750 mM of sucrose significantly masked each concentration of Q-HCl. The interlick interval was significantly reduced when sucrose was added to Q-HCl concentrations.

As shown in figures 12-16, there were no significant effects of any stimulus on the latency to approach and lick the spout. There was no significant main effect of latency to first lick for water or the four concentrations of FDT during 30-second trials. There was no significant main effect of latency to first lick for increasing concentrations of Q-HCl during 30-second trials. There was no significant main effect for latency to first lick when increasing FDT concentrations were compared to increasing concentrations of Q-HCl during 30-second trials. There was no significant main effect for latency to first lick for the increasing FDT concentrations alone or with 250 or 750 mM sucrose during 30-second trials. There was no significant main effect for latency to first lick when increasing Q-HCl concentrations alone or with 250 or 750 mM sucrose during 30-second trials.

Discussion

The purpose of this study was to assess FDT containing LPV/r in order to determine if the bitterness could be masked in order to be less aversive. Results showed that there were no significant effects of any stimulus on the latency to approach and lick the spout. As hypothesized, sucrose at 750 mM effectively masked the bitterness of the quinine hydrochloride
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(Q-HCl) stimulus at all doses. 250 and 750 mM sucrose produced an increase of licking. However, the addition of sucrose to FDT containing LPV/r showed no effect on oromotor responses. These results suggest that there might be something in the FDT containing LPV/r that is aversive, besides bitterness alone, which deters rats from licking even with the addition of sucrose.

Results show that there is a threshold for averseness with FDT containing LPV/r (Figure 1). As the concentration of FDT to water increases, the standardized lick ratio decreases. FDT 1:30 is below the threshold as to when the FDT becomes aversive. The rats’ licking decreases at the FDT 1:3 ratio and then stays the same for the FDT 1:2 and 1:1 ratios. However, the FDT 1:30 ratio is the body weight adjusted ratio, meaning this ratio for rats is equally compared to the ratio that is given to human children. A human child would receive the FDT 1:1 ratio. Rats weigh about 30 times less than a human child, so their concentration is 30 times less than what a child would receive. These results suggest that rats might be more sensitive to the higher FDT concentrations than a child would be; since the body weight adjusted concentration is much lower than the typical dosage for a child.

In Figure 4, there were no significant differences between the standardized lick ratio of the FDT concentrations and Q-HCl concentrations. Q-HCl concentrations were expected to be very good estimates of the averseness of the FDT concentrations. Therefore we expected that the addition of sucrose to the highly comparable averse concentrations should yield the same results. However, we did not see the similar effects between the two averse concentrations. Contrary to FDT concentration, 250 and 750 mM of sucrose both effectively masked the aversive Q-HCl concentrations even at the highest concentration of Q-HCl. In Figure 6, the highest Q-HCl concentration (2.5 mM) with the addition of 750 mM of sucrose reached and average
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standardized lick ratio of about 0.65, whereas in Figure 5 the highest FDT concentration (1:1) with 750 mM of sucrose reached an average standardized lick ratio of only about 0.06, and the only closest standardized lick ratio to the highest Q-HCl concentration was around 0.26 for rat BM04 in FDT 1:1 + 750 mM sucrose. This is a very large difference. As you can see in Figure 9, even the interlick interval for both averse concentrations showed no significant differences, yet sucrose only decreased the oromotor responses, and overall interlick interval, in concentrations of Q-HCl and not FDT. The interlick interval is associated with the palatability of a taste solution and when rats encounter an aversive stimulus they exhibit stereotypical oromotor responses such as gaping and tongue protrusions in response to the negative stimulus. Unlike Q-HCl, FDT’s containing LPV/r are averse enough to maintain stereotypical oromotor responses even when 750 mM of sucrose is added.

We provide several explanations and potential hypotheses for why 250 mM and 750 mM of sucrose effectively masked the aversive Q-HCl concentrations and not the FDT concentrations. Non-taste aversive stimuli in FDT containing LPV/r such as an aversive trigeminal component (astringency, texture, or pain) would not necessarily be masked by sucrose. In order to test this hypothesis we could condition a taste aversion to FDT’s containing LPV/r in rats and then we could compare this aversion to known stimuli with non-taste aversive stimuli in order to pinpoint where these differences are coming from. We then could work on developing a method to manipulate the specific or multiple non-stimuli in order to increase palatability and overall increases in the standardized lick ratio and interlick interval. Another explanation for the lack of generalizable results could be that there is floor effect. FDT 1:1 and 2.5 mM Q-HCl have similar licking patterns but FDT 1:1 might actually be several times more aversive, which could be why masking with sucrose was ineffective. Rats might have a difficult
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Time differentiating between an averse and highly aversive stimulus, which might be why the standardized lick ratios look similar for FDT 1:1 and 2.5 mM Q-HCl. We could test this hypothesis by adding more averse concentrations of Q-HCl to see if there is a generalization and overall floor effect. If there were a floor effect, we would predict that there would be no difference between the higher concentrations of Q-HCl. We could also test a larger range of FDT containing LPV/r dilutions in order to detect a threshold of avoidance. Another explanation might be the presence of non-taste sensory cues prompting a specific aversive stimulus. Rats could have learned to associate non-taste sensory cues with the averseness of FDT containing LPV/r alone then they may continue to avoid LPV/r even in the presence of sucrose. Non-taste sensory cues such as olfactory cues, or textural cues such as viscosity could have prompted this potential association. For example, FDT 1:1 and 2.5 mM Q-HCl were comparably similar in averseness but the FDT containing LPV/r could have had a non-taste sensory cue such as a specific smell or consistency that the rat learned over several licks and later used this association of the non-taste cue to prompt the rat to lick less. Therefore FDT containing LPV/r and Q-HCl averseness might well have been very similar but the FDT containing LPV/r might have elicited cues to stop licking. We could test this by exposing naïve rats to the sucrose-masking stimulus first before they get exposed to FDT alone. Of the possible explanations for the results, we support the first explanation, which proposes that there is an additional negative hedonic stimulus associated with FDT containing LPV/r beyond its aversive taste. The lack of an effect of sucrose to reduce the interlick interval when added to FDT supports a non-taste mediated aversive effect of FDT containing LPV/r.

In Figure 2, rats significantly differ in their standardized lick ratio between each FDT ratio whereas in Figure 3, rats elicited no significant differences between Q-HCl concentrations.
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This might be why when we add sucrose we see a significant difference between the two stimuli. Q-HCl concentrations seem to be generalizable therefore rats don't discriminate between Q-HCl as much as the FDT. This also helps show that FDT concentrations are more averse between each other than the Q-HCl concentrations. Sucrose could provide the mask needed to increase the over generalization for Q-HCl concentrations. Figure 6 shows Q-HCl concentrations with 750 mM sucrose roughly have comparable average standardized lick ratios whereas in Figure 5 the standardized lick ratios for FDT concentrations are more variable, especially at the highest concentration.

Martinez and Riordan (2010) state that ritonavir suspension has an extremely poor taste and even the co-formulation with LPV still has poor taste. Ritonavir might be the reason why FDT’s containing LPV/r are so highly aversive. The researchers also provide evidence to support that low dose LPV/r tablets increased palatability in children, which might prove that reducing ritonavir increases tolerance and also prove why FDT containing LPV/r is more averse than Q-HCl (Martinez & Riordan, 2010). We could test this hypothesis by using LPV/r, LPV alone, and ritonavir alone to see if ritonavir is more aversive than LPV, and whether LPV with ritonavir multiplies the aversive effect. We would predict ritonavir is the aversive component in FDT’s containing LPV/r. After that we could manipulate the ritonavir’s taste, non-taste aversive stimuli, or non-taste cues in order to increase drug tolerability and pediatric adherence.

Future studies that our researchers are interested in conducting would be to replicate these tests using the placebo FDT that lacks the LPV/r. Having brief-access licking data for the placebo FDT would be a nice compliment to a long-term solution and a food consumption test paradigm. This would hopefully provide more evidence that rats are indeed avoiding the LPV/r and not some component of the FDT solution.
References


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FactsheetIATT_WHO_UNICEF_lopinavir_eng.pdf
Figure 1. The standard lick ratios compared to water and four FDT concentrations, FDT 1:30, FDT 1:3, FDT 1:2, and FDT 1:1. There was no significant difference between the lowest FDT concentration 1:30 and water. The star symbol on the graph shows that there is a significant difference ($p < .01$) between water/FDT 1:30 and FDT 1:3, 1:2, and 1:1, indicating that the higher concentration of FDT, the more aversive the solution. The star above FDT 1:1 shows that licking concentrations was significantly lower ($p < .01$) than all other concentrations.
Figure 2. The standard lick ratios across the three strongest FDT concentrations, FDT 1:3, FDT 1:2, and FDT 1:1. The plus symbol indicates that there was a significant difference ($p < .05$) between FDT 1:3 and FDT 1:2. The star indicates that there is a significant decrease ($p < .01$) in licking for FDT 1:1, and FDT 1:2 and 1:3.
Figure 3. The standard lick ratios compared to water and three Q-HCl concentrations, 1.5, 2, and 2.5. The star symbol represents that there is a significant decrease ($p < .01$) in licking for the three Q-HCl concentrations in comparison to water. Pairwise comparisons were made in order to show that there were no significant differences in the three Q-HCl concentrations and licking patterns.
Figure 4. The standard lick ratios when observing the three strongest concentrations of FDT in comparison to the three strongest concentrations of Q-HCl.
Figure 5. Licks to the concentrated FDT alone and with 250 or 750 mM sucrose mask during 30-second trials. Error bars represent the standard error of the mean.
Figure 6. Licks to Q-HCl alone and with 250 or 750 mM sucrose during 30-second trials. Error bars represent the standard error of the mean. Stars indicate a significant increase in licking when sucrose was added to the Q-HCl as when compared to Q-HCl alone ($p < .01$). The plus symbol indicated a significant increase in licking to the masked Q-HCl in comparison to Q-HCl alone ($p < .05$).
Figure 7. The average interlick intervals for water and four concentrations of FDT during 30-second trials. Stars represent a significant decrease in interlick intervals for water and FDT 1:30.
Figure 8. The average interlick interval (ms) for water and Q-HCl concentrations in a 30-second trial is presented above. Stars represent interlick intervals significantly ($p < .01$) greater than water. The plus symbol represents interlick intervals significantly greater than water, $p < .05$. Standard error is represented through the error bars attached to each column.
Figure 9. Interlick interval comparison between FDT and Q-HCl concentrations. There were no significant differences in the interlick interval for each increasing concentration. Standard error is represented through the error bars attached to each column.
Figure 10. Interlick interval for FDT concentrations alone, with 250 mM or 750 mM of sucrose. The sucrose-masking stimulus had no effect in decreasing the interlick interval of the FDT concentrations. Standard error is represented through the error bars attached to each column.
Figure 11. Interlick interval for Q-HCl concentrations alone, with 250 mM or 750 mM of sucrose. The sucrose-masking stimulus significantly decreased the interlick interval when added to Q-HCl. The star represents the significant difference between 250 mM of sucrose on the 2.5 concentration of Q-HCl when compared to 750 mM of sucrose, $p < .01$. The plus symbols represents the significant differences ($p < .05$) between Q-HCl concentrations alone compared to the addition of 750 mM of sucrose.
Figure 12. Comparison of latency until the first lick for water as well as the four concentrations of FDT during 30-second trials.
Figure 13. Latency until the first lick for increasing concentrations of Q-HCl during 30-second trials.
Figure 14. Comparison of latency until the first lick for the increasing FDT concentrations and the increasing Q-HCl concentrations during 30-second trials.
Figure 15. Latency until the first lick for increasing FDT concentrations alone and with 250 or 750 mM sucrose during 30-second trials.
**Figure 16.** Latency until the first lick for increasing Q-HCl concentrations alone and with 250 or 750 mM sucrose during 30-second trials.