



# A New Method of Characterizing the Buccal Dissolution of Drugs

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## INTRODUCTION

Over the last several years there has been a great increase in interest for liquid and dissolve-in-the-mouth dosage forms. This interest is spurred by the promise of improved patient compliance compared to tablets and capsules, that have to be swallowed whole. Unfortunately, such dosage forms bring along new problems – taste and characterization. When a drug is even partially dissolved in the mouth the patient tastes the drug, and if it is objectionable the whole aim of improved compliance is lost. Even when taste is not an issue, the characterization of dissolution in the mouth is not easily done by current methodology, such as variants of the USP dissolution test. The reason for this is the speed of disintegration/dissolution compared to typical dosage forms designed to be swallowed whole.

A thorough search of both the patent and open literature reveals no *in vitro* systems to evaluate the buccal dissolution of such systems.

In this paper, we describe a novel dissolution testing system<sup>1</sup> that is capable of characterizing buccal dissolution. It has been demonstrated to correlate with human taste perception. The method is rapid, repeatable, and can be applied to all the common liquid and dissolve-in-the-mouth solid dosage forms.

## METHOD FUNDAMENTALS

There are a number of factors that are unique to characterizing buccal dissolution that do not apply to GI dissolution. They are:

- Small volume
- Short residence time
- Solids transfer
- Composition
- Incomplete dissolution

Most of the USP dissolution tests use large volumes of solution - defined as ‘sink conditions’; the aim is to get complete dissolution of the active ingredient. For buccal dissolution the volume of saliva is very small compared to that of the stomach and the residence time in the mouth is also very short, the bulk of the dosage form being swallowed within a minute (with the exception of lozenges). In addition, complete dissolution is not usually required, or even desirable. For example for fast-melt tablets such as the Zydis® system<sup>2</sup> what is desired is actually complete disintegration not dissolution. This means that the removal of finely divided solids from the test vessel is absolutely critical to get any type of bio-relevant test.

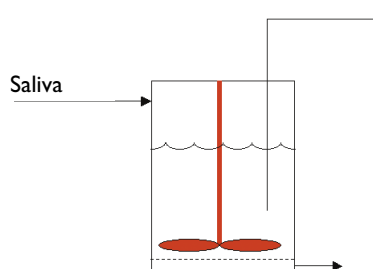


Figure I - Schematic of Buccal Dissolution Apparatus

The system reported here is able to address all these factors. It comprises a single, stirred, continuous flow-through filtration cell that includes a dip tube designed to remove finely divided solid particles. Fig I shows the system schematically. Filtered solution is removed continuously and used to analyze for dissolved drug. The volume of liquid in the cell is approximately 10ml and fluid is pumped through it at about 6 ml/min. This gives a residence time in the cell of approximately 100 secs for 63% of the dosage form and gives almost complete removal in about 8 minutes. Approximately two thirds of the flow exits via the dip-tube and the other third exits through the filter for analysis.

<sup>1</sup>Patent Application filed

<sup>2</sup> Zydis is a registered tradename of R. P. Scherer. Claritin RediTabs is a tradename of Schering Corporation.

In use the cell is filled and flows are set-up first and allowed to reach steady state, then the dosage form (solid, liquid, suspension, or powder) is introduced. The filtered sample is either analyzed in-line (eg by uv flow-thru cell) or samples are collected in a fraction collector for later analysis.

In order for this test to give meaningful results it is necessary to use a dissolution fluid that simulates saliva. There is no USP recommended simulated saliva, so the composition used in these studies was based on published ranges<sup>3</sup>. The composition used is shown in Table I

KH <sub>2</sub> PO <sub>4</sub>	12 mM
NaCl	40 mM
CaCl <sub>2</sub>	1.5 mM
NaOH	to pH 6.2

## RESULTS

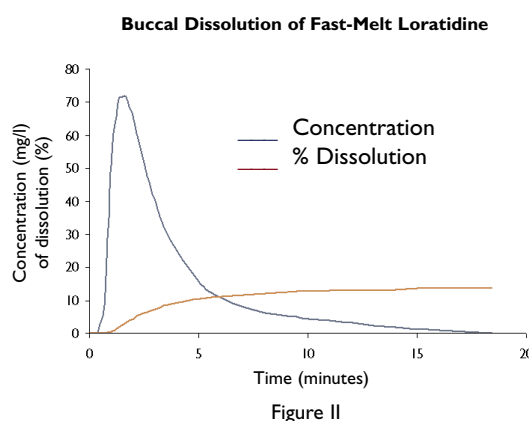
The equipment has been demonstrated using three different formulations:

- Claritin® RediTabs®
- Liquid formulation of paroxetine
- Dissolve-in-the-mouth tablets of Drug X<sup>4</sup>

Claritin Reditabs are fast-melt tablets of loratidine that use the Zydis technology. Although this is not a taste-masked formulation this dosage form was used to demonstrate the equipment's ability to handle this type of dosage form. The results are shown in Fig II and demonstrate a couple of interesting facets of this test method. Firstly, there is a peak in the concentration-time curve. This peak is a characteristic of all the dosage forms that we have tested so far and is an inevitable result of a continuous, flow-thru system such as this where a compound is added in a single bolus. For a particular dosage form the time at which this peak occurs is approximately constant at constant flow rate, but its height (i.e. peak concentration) varies with the amount of drug that dissolves and the speed with which it dissolves. It is this parameter, peak concentration, that we have found to correlate with taste.

The next important point to note in Fig II is the % Dissolution curve. Note that only about 13% of the

loratidine actually dissolves. Unlike GI dissolution testing this is not a 'bad' result. However, the amount that dissolves will affect the taste of the fast melt tablet. If taste was an issue for this formulation then clearly this test method could be used to quantify the amount dissolved for a variety of formulations at an early stage in the development program and the best ones selected for further development.

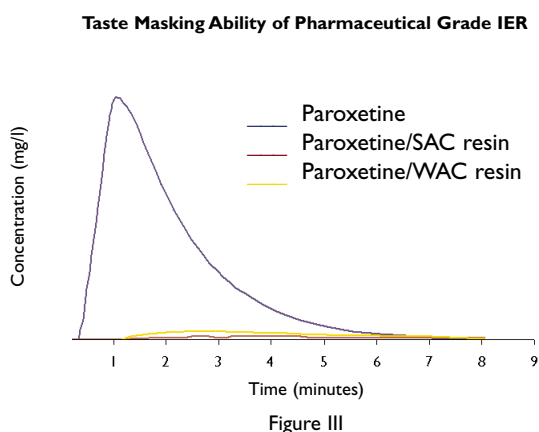


The next example that we studied was a taste-masked liquid formulation of paroxetine that used ion exchange resins to achieve the taste masking. Data on the relative taste of some of the formulations tested during development had been published<sup>5</sup> so we were able to compare our results with the published data.

Three formulations were tested:

- A - paroxetine solution
- B - a complex of paroxetine and a strongly acid cation exchange resin
- C - a complex of paroxetine and a weakly acidic cation exchange resin

From a taste masking point of view, it was reported that B was better than C, but that the taste of C was still acceptable.



<sup>3</sup> Ritschel and Thompson, Methods and Findings in Experimental and Clinical Pharmacology, 5, 511-525, 1983

<sup>4</sup> The nature of Drug X cannot be revealed for reasons of confidentiality

<sup>5</sup> D. P Elder et al, 'Development of a Palatable Liquid Formulation of a Bitter Tasting Drug using Ion exchange Resins for Taste Masking', Proceedings of IEX 2000. Ion Exchange at the Millennium., 307 - 313, 2000.

The results of our buccal dissolution test are summarized in Fig III. Firstly, for the solution one sees the characteristic curve with a peak concentration of about 170 mg/l.

The two taste-masked formulations, B and C, have very much lower peak concentrations, indicating that much less paroxetine dissolved. The peak concentration for B is significantly lower than that for C. These results correlate exactly with the published taste perception.

It is interesting to note that the time to the peak concentration is longer for B and C than for A. This is because the paroxetine is very slowly being released from the complexes B and C and what the test is detecting is the release from the solid that remains in the cell the longest. This is not a trivial result because there will inevitably be some material that stays in the mouth after the first swallow that leave an ‘after-taste’.

It is possible to use the data from these tests to quantify the taste-masking efficacy of the formulation. The actual peak concentrations for B and C were 2 and 6 mg/l, respectively, while that for A was about 170 mg/l. Therefore one could quantify the taste masking in terms of the reduction in concentration relative to the same amount of drug added in solution. In this case the taste masking efficacies are 98.8% for B and 96.5% for C. While this can be an useful way to quantify taste-masking we propose an alternative later in this paper (‘Taste Equivalent Dose’).

The third example is a dosage form of a drug, referred to here as Drug X for reasons of confidentiality. In these test a series of three formulations were characterized in a ‘blind test’. At the time of the test the only information available to the analyst was the amount of drug in each, and a calibration curve for analysis of the drug by UV spectroscopy.

The three formulations were as follows:

- Formulation A – 5mg Drug X
- Formulation B – 5 mg Drug X
- Formulation C – 0.1mg Drug X

The results of the tests are shown in Fig IV The first point to note is the curve for pure drug X. It has the characteristic shape with a peak concentration of about 55 mg/L, with the time to peak concentration of about 1.5 minutes.

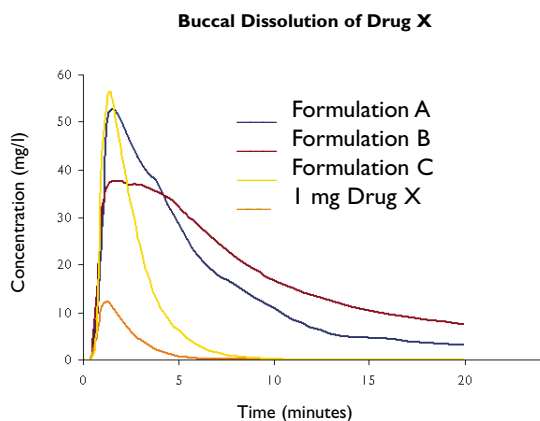


Figure IV

Formulation C has almost the same curve shape, only at lower concentrations. The ratio of peak concentration are about the same as the ratio of the amount of drug, i.e. approx 5:1. Formulations A and B have distinctly broader curves and peak concentrations equal to or less than that of 1mg of pure drug, even though they contain 5 mg of drug. Clearly, this indicates some level of taste-masking for A and B. This data would predict that B has less taste than A, although the difference is not dramatic. We were not able to calculate the taste-masking efficacy in the same way as for the previous example because 5 mg of drug X gave a uv absorbance that was off-scale.

Based on these results the following conclusions were made:

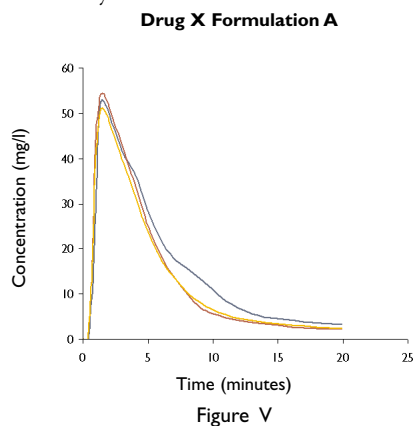
- C is in not taste-masked
- A and B are taste-masked
- The order of taste intensity is A>B>C

After the tests were completed the conclusions were compared with formulation information and the results of human taste panel evaluations (Table II).

The buccal dissolution tests, the formulation information and the taste panel results correlate exactly. Also, since Formulation C represented the maximum dosage with acceptable taste, the data also predicts that neither A nor B would have acceptable taste.

Table II. Evaluation of Drug X formulations		
Formulation	Taste-masked	Taste panel
A	Yes	Not acceptable, worst than B
B	Yes	Not acceptable, better than A
C	No	Maximum acceptable

In these experiments the repeatability of the test was also determined by running multiple tests. One set of such data for Formulation A is presented in Fig V. This shows that the repeatability of the peak concentration is good. Note that the observed variability will include a contribution from unit-to-unit variability.



## TASTE EQUIVALENT DOSE

The test method described in this paper allows for the quantification of the taste of a formulation. However, there are a number of different ways in which it can be expressed, for example the % reduction in peak concentration, as described in the second example. However, there are problems associated with that approach, not least of which is that the peak concentration for a completely dissolved, full dosage sample may be outside the conveniently analyzable range. In addition, the taste masking efficacy needed to obtain some target dose will vary with the dose amount.

A more practical measure of the taste masking efficacy is the 'Taste Equivalent Dose' (TED). The TED is defined as the dose of pure, dissolved drug that has the same taste as the dosage form tested.

For our purposes, peak concentration is used as a surrogate for the taste so the definition becomes:

*The TED of a dosage form is the dose of pure, dissolved drug that has the same peak concentration.*

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This concept is used by determining a TED calibration curve by injecting varying amounts of pure, dissolved drug and plotting peak concentration vs the amount added (the dose). The TED of any formulation of the drug can then be estimated from its peak concentration in the test using this calibration curve. In practice we have found that the TED curve is approximately linear.

As an example, the TED curve for paroxetine gave the regression equation:

$$Dose(mg) = 0.0292 \times Peak\ Conc(mg/l)$$

Therefore, the TED's for the paroxetine formulations B and C in the second example are 0.68 mg and 0.95 mg respectively.

## CONCLUSION

This paper presents the first published *in vitro* test for buccal dissolution that correlates taste perception. The method characterizes the amount of a drug that dissolves during passage through the mouth. The data from this method allows the prediction of the intensity of the taste of a dosage form relative to another dosage form or of a performance target. The method is particularly suited for evaluating taste masking. It is rapid, taking only about 20 minutes per test and is repeatable.

The method could be used as a QC test to ensure dosage uniformity, and as a development tool to optimize formulations before human testing, thus reducing the amount of human testing needed.

## ACKNOWLEDGMENTS

The authors wished to acknowledge the contributions to this work made by the following people.

Christina Hann *ex Rohm and Haas*  
Simon Bellamy *Rohm and Haas*

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