A Matter of Taste

The bitter taste of orally delivered drugs can be masked in a number of different ways, and interest in developing this area has surged recently. However, a complementary blend of techniques may be the way forward

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Over the last few years, there has been a tremendous increase in the interest for liquid and 'dissolve-in-the-mouth' dosage forms. In this area, taste is extremely important to encourage patient acceptability and compliance. Acceptable taste can help to determine market penetration and the commercial success of a new active pharmaceutical ingredient (API) or a new dosage form. Unfortunately, the majority of orally administered, moderately water-soluble drugs are inherently very bitter. This is especially problematic with paediatric suspensions, since children appear to be more sensitive to taste than adults. Therefore, the ability to mask bitter-tasting APIs is one of the biggest challenges facing drug formulators today.

Ion Exchange Complexation

A variety of techniques are available for masking bitter-tasting APIs including: complexation with ion exchange resins; coating APIs with materials such as starch, povidone, gelatin, methylcellulose, ethyl cellulose, hydroxyl propyl methyl cellulose (HPMC) and shellac; the addition of natural flavours or sweeteners, such as peppermint, lemon oil, clove, balsam, aspartame and sodium saccharine; spray drying to prepare microparticles using hydrophilic polymers such as HPMC and polyvinyl pyrrolidone (PVP); complexation with cyclodextrin; and microencapsulation.

This article focuses primarily on the use of complexation with ion exchange resins. This technique has been used to successfully mask bitter drugs such as Tinidazole, Topiramate, Ondansterone and Piroxicam (1). Typically, only

dissolved substances elicit taste sensation in the buccal cavity. Since ion exchange resins are insoluble, the API is not released during the quick passage through the mouth, but in most cases is rapidly released in the gastro-intestinal tract. As a result, the bitter taste of an API is not sensed when the drug is complexed with an insoluble ion exchange resin as a resinate.

The complexation technique is attractive for several reasons:

- Ion exchange resins have well-established safety profiles, regulatory support, and have been used as excipients for over 60 years

- Highly cross-linked ion exchange resins work extremely well in suspension formulations, unlike soluble polymers

- Ion exchange technology can also provide stabilisation, and modified and extended release of the API, if desired

Ion exchange technology has the added ability to provide a section of release profiles from immediate release to modified release of the API. This is achieved through the selection of

different ion exchange chemistries. A list of ion exchange resins that can be used as functional excipients is shown in Table 1, along with their potential applications in oral formulations.

API Pre-Formulation

Pre-formulating an API with an ion exchange resin for taste masking is a fairly straightforward process. A solution of the drug is prepared in deionised water (or suitable organic solvent for water-insoluble APIs). The resin is then added to the solution. Typically a 1:1 ratio of resin to drug can be used for the initial conditions, and the ratio can be optimised with subsequent development work. The loaded resinate can then be separated from the remaining drug solution using filtration, and resulting resinate wet cake can be dried and formulated into the desired final form.

Release of API *in situ*

An example of the mechanism of release of a weakly acidic API from a strong anion exchange resin is shown in Figure 1 (see page 60). As the oral formulation passes through the buccal cavity, the API remains bound to the ion exchange resin. As a result, the API

Table 1: Ion exchange resins used as functional excipients	
Compendial name	Function in the dosage form
Polacrilex resin	Taste masking for free base drugs, drug stabilisation
Polacrilin potassium resin	Taste masking for ionised basic drugs, tablet disintegration
Sodium polystyrene sulfonate resin	Extended release, drug stabilisation, taste masking for free base or ionised basic drugs
Cholestyramine resin	Extended release, drug stabilisation, taste masking for acidic drugs

does not create a taste sensation in the mouth of the patient. Once the drug passes into the stomach, the shift in pH and increase in ionic concentration promotes the rapid release of the API from the ion exchange resin.

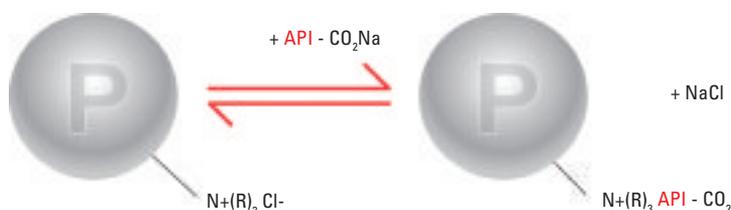**Figure 1:** Mechanism of release from ion exchange resin

Table 2: Composition of simulated saliva

KH_2PO_4	12mM
NaCl	40mM
$CaCl_2$	1.5mM
NaOH	to pH 6.2

Evaluation of Masking Bitter Taste

Assessment of masking bitter taste is one important quality control parameter of an oral pharmaceutical formulation, and this assessment can include either *in vitro* or *in vivo* methods such as human taste panels or electronic tongues.

Most of the United States Pharmacopeia (USP) dissolution tests use large volumes of solution – defined as 'sink conditions'; the aim is to get complete dissolution of the API. For buccal dissolution, the volume of saliva is very small compared to that of the stomach, and 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, what is desired is actually complete disintegration rather than 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.

The dynamic buccal dissolution system described here can predict the intensity of the taste of the dosage, and is an improvement to the standard USP test.

It comprises a single, stirred, continuous flow-through filtration cell that includes a dip tube designed to remove finely divided solid particles. Filtered solution is removed continuously and used to analyse for dissolved drug. The volume of liquid in the cell is approximately 10ml and the fluid is pumped through it at about 6ml/min. This gives a residence time of approximately 100 seconds for 63 per cent of the dosage form and gives almost complete removal in about eight minutes. Approximately two-thirds of the flow exits via the dip tube and the other third exits through the filter for analysis.

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 analysed in-line – for example by ultraviolet flow through cell – or samples are collected in a fraction collector for later analysis.

In order for the test to give meaningful results, it is necessary to use a dissolution fluid that simulates saliva. Table 2 shows the composition of the simulated saliva used in these studies, based on published ranges (2).

TED Calibration

The test method described above 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 the purposes of these analyses, peak concentration is used as a surrogate for the taste. In particular, the Taste Equivalent Dose (TED) of a dosage form is the dose of a pure, dissolved drug that has the same peak concentration. This concept is used by determining a TED calibration curve by injecting varying amounts of pure, dissolved drug and plotting peak concentration versus the amount added (the dose). The TED of any formulation can then be estimated from its peak concentration in the test using this calibration curve.

In this first example, two different resin chemistries were tested for taste masking effect. Pseudoephedrine HCl was loaded on either a weak acid cation exchange resin, polacrilin potassium, or a strong acid cation exchange resin, polystyrene sulfonate, to create the respective resinates. Figure 2 demonstrates the effectiveness of both resins in reducing the taste profile. The polacrilin potassium resinate does not mask as effectively as the

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strong acid cation polystyrene sulfonate resin. However, the strong acid cation exchange resin will also modify the release of the pseudoephedrine to give a more extended release profile (data not shown).

Complementary techniques may be employed to improve taste masking and eliminate changes to the release profile. Figure 3 helps to show the complementary nature of coating and ion exchange technology for taste masking of hydrocodone bitratrate. In this example, a 30mg dose of the API was first loaded onto the weak cation exchange polacrilex resin and evaluated with the buccal dissolution assay. The loaded resinate was also coated with 10 per cent of SureRelease and evaluated with the same assay. The coated resinate provides a further slight reduction in taste.

Conclusion

Complexation with ion exchange resins is a well-established technique that can be used to mask strongly bitter-tasting APIs. Multiple resin chemistries are available as functional excipients so that acidic and basic drugs can effectively disguise bitter tastes.

Additionally, masking of bitter tastes can be evaluated by a quick and simple *in vitro* dynamic dissolution assay. The data from this method enables a prediction of the intensity of the taste of dosage form relative to another dosage form or a performance target.

References
1. Sikandar, Malviya and Sharma, *European Journal of Biological Sciences* 3: pp67-71, 2011
2. Ritschel and Thomson, *Methods and Findings in Experimental and Clinical Pharmacology* 5: pp511-525, 1983

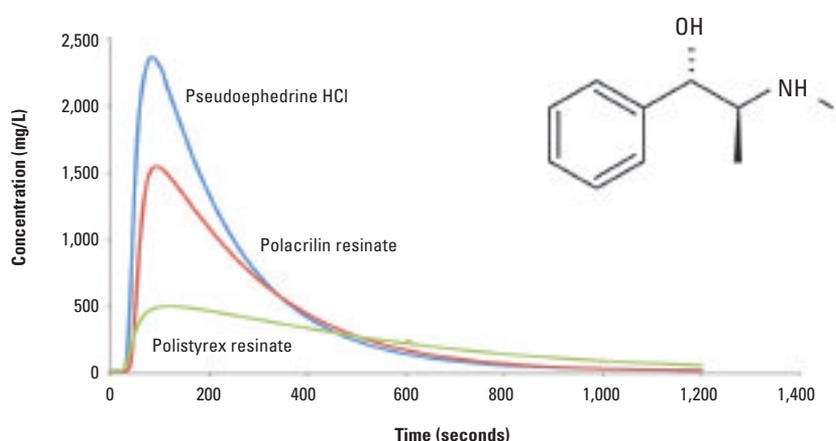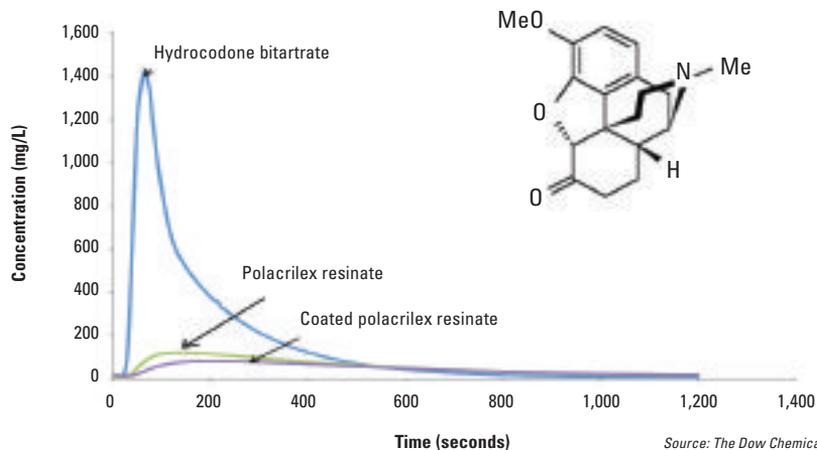**Figure 2:** Taste masking results for pseudoephedrine HCl

Figure 3: Taste masking results for hydrocodone bitartrate

Source: The Dow Chemical Company

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