TASTE MASKING OF PHARMACEUTICAL ACTIVES USING ION EXCHANGE RESINS

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ABSTRACT

Taste is an important parameter in case of administering drugs orally. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. The problem of bitter and obnoxious taste of certain drugs is a challenge to the pharmacist in the present scenario. Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance and products palatability especially in the paediatric and geriatric population. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which intern decides the commercial success of the product. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. Two approaches are commonly utilized to overcome the bad taste of the drug. The first includes reduction of drug solubility in the saliva and second approach is to alter the ability of the drug to interact with taste receptor. To achieve the same various methods have been explored. Some of them are coating of drug particles, formation of inclusion complexes, molecular complexes of drugs with other chemicals, solid dispersions, melting method, micro encapsulation, prodrugs approach, mass extrusion methods and ion exchange resins. This paper particularly reviews the role of the ion exchange resins to mask undesirable taste of the bitter drugs with their potential applications.

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INTRODUCTION

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor’s product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability.[1]

There are numerous pharmaceuticals that contain actives, which are bitter in taste. With respect to OTC preparations, such as cough and cold syrups, the bitterness of the preparation leads to lack of patient compliance. The problem of bitter and obnoxious taste of drug in paediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste.

Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor.

THE SENSE OF TASTE

Taste is the ability to respond to dissolved molecules and ions. Our tongue detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside.

Human have around 10,000 taste buds, a single taste bud contains 50-100 taste cells. Each taste cells receptors on its apical surface. These are transmembrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter.

CHALLENGES OF DEVELOPING PALATABLE FORMULATIONS

Development of a palatable formulation can be associated with significant challenges that are discussed below:

a. The most relevant selection criteria are safety, tolerability and efficacy of the compound which are based on non-clinical testing, and physico-chemical properties such as solubility, permeability, stability and crystallinity [2].

b. Adult dosage forms can be easily taste masked by encapsulation or film coating techniques, if required.

c. There is a lack of robust and reliable techniques for early taste screening of compounds with limited toxicity data.
d. The current understanding of the structure–taste relationships of pharmaceutically active molecules is limited.

The perception of taste of medicines has been shown to be different between adults and children and will probably differ between healthy and sick children [3]. Ideally taste should be assessed in children, but there may be some ethical concerns to perform taste studies in healthy children unless the study is a ‘swill and spit’ one with drugs known to have a good safety profile [4].

FACTORS AFFECTING SELECTION OF TASTE MASKING TECHNOLOGY

Different taste masking technologies have been used to address the problem of patient compliance [5]. With aggressively bad tasting medicaments even a little exposure is sufficient to perceive the bad taste. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs such as quinine, celecoxib, etoricoxib, antibiotics like levofloxacin, Sweeteners could not achieve taste masking of oral formulation of ibuprofen due to its dominating taste[6]. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions [7]. Viscosity enhancers can complement the taste masking efficiency. Oral suspension containing viscosity enhancers can masquerade the objectionable taste, which arises from the leakage of drug from the coated medicaments or microcapsules.

ION EXCHANGE RESIN

Ion exchange resins have been used to help formulate pharmaceuticals since the late 1950's. During that time they have proved to be safe and effective excipients and are now used in many commercial formulations throughout the world. In this article we will look at some of the common problems faced by formulators and how using ion exchange resins may be able to solve them. Ion exchange resins are insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions with aqueous solutions surrounding them. The equation in Figure I shows a representative reaction when drugs are loaded onto or released from the resins. A drug ion and an inorganic ion are exchanged. The reaction is an equilibrium, the position of which will depend on many factors including salt concentration in the aqueous phase. This property allows drugs to be loaded onto resins (forming drug resinates) and then released in vivo by the salts present in GI fluids. The resinates possess physical properties similar to the resin. These two properties- drug release and physical properties - can be manipulated to create many variations of use to the formulator.

One of the popular approaches in the taste masking of bitter drugs is based on IER. IER are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium [8-9]. Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. The long-term safety of IER, even while ingesting large doses as in the use of cholestyramine to reduce cholesterol is an established unique advantage of IER due to the fixed positively or negatively charged functional groups attached to water insoluble polymer backbone [10]. These groups have an affinity for oppositely charged counter ions, thus absorbing the ions into the polymer matrix. Since most drugs possess ionic sites in their molecule, the resin's charge provides a means to loosely bind such drugs and this complex prevents the drug release in the saliva, thus resulting in taste masking. For taste masking
purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.

CLASSIFICATION OF IER

IERs contain positively or negatively charged sites and are accordingly classified as either cation or anion exchanger. The functional group in cation exchanger and anion exchanger undergoes reaction with the cations and anions of the surrounding solution respectively[11]. The strong cation exchanger contains sulphuric acid sites whereas weak cation exchangers are based on carboxylic acid moieties. The strong anion exchange resins have quaternary amine ionic sites attached to the matrix, whereas weak anion exchanger has predominantly tertiary amine substituents. Details of IERs are available which are summarized in Table - 1.

Table 1- Examples of Ion Exchange Resin Drug Complex

<table>
<thead>
<tr>
<th>Resin</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberlite™ Irp64, Irp69</td>
<td>Dextromethorphan, Ranitidine</td>
</tr>
<tr>
<td>Amberlite™ Irp88</td>
<td>Talampacillin-HCl, Paroxetine</td>
</tr>
<tr>
<td>Amberlite™ Ir120</td>
<td>Dimenhydrinate</td>
</tr>
<tr>
<td>Amberlite™ Irc50</td>
<td></td>
</tr>
<tr>
<td>Amberlite™ Ir400, Ir4b</td>
<td></td>
</tr>
<tr>
<td>Indion 204</td>
<td>Ofloxacin, Norfloxacin</td>
</tr>
<tr>
<td>Indion 214</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Indion 234</td>
<td>Ciprofloxacin, Chloroquin phosphate</td>
</tr>
<tr>
<td>Kyron t-104</td>
<td>Paroxetine, Cefpodoxime proxetil</td>
</tr>
<tr>
<td>Kyron t-114</td>
<td></td>
</tr>
<tr>
<td>Kyron t-134</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Dowex 1</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Dowex2</td>
<td></td>
</tr>
<tr>
<td>Dowex 50</td>
<td></td>
</tr>
<tr>
<td>Doshion p544(r)</td>
<td></td>
</tr>
<tr>
<td>Duolite ap 143</td>
<td></td>
</tr>
<tr>
<td>Tulsion 335</td>
<td></td>
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<tr>
<td>Tulsion 339</td>
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</tbody>
</table>
Ion exchange resins are broadly classified into two main Categories, as Cation exchange resins and anion exchange Resins (Fig. 1).

1. Cation Exchange Resins

They are those resins whose exchangeable ions are positively charged: Cation exchange resins are prepared by the copolymerization of styrene and divinyl benzene and have sulfonic acid groups (-SO₃H) introduced into most of the benzene rings. The mechanism of Cation exchange process can be represented by the following reaction:

\[ \text{Resin} - \text{ex}^+ + \text{C}^+ \rightarrow \text{Resin} - \text{ex}^+ + \text{C}^+ \]

Where, Resin- indicates a polymer with SO₃⁻ sites available for bonding with exchangeable Cation (ex⁺), and C⁺ indicates a Cation in the surrounding solution getting exchanged.

Cation exchange resins can be further classified into:

(a) **Strong Acid Cation Exchange Resins**

Strong acid resins are so named because their chemical behavior is similar to that of a strong acid. These resins are highly ionized in both the acid (R-SO₃H) and salt (RSO₃Na) form of the sulfonic acid group (-SO₃Na). They can convert a metal salt to the corresponding acid by the reaction:

\[ 2(R-SO_3 \text{H}) + \text{NiCl}_2 \rightarrow (R-SO_4) \text{Ni} + 2\text{HCl} \]

The hydrogen and sodium forms of strong acid resins are highly dissociated, and the exchangeable Na⁺ and H⁺ are readily available for exchange over the entire pH range. Consequently, the exchange capacity of
strong acid resins is independent of the solution pH. These resins would be used in the hydrogen form for complete deionization; they are used in the sodium form for water softening (calcium and magnesium removal). After exhaustion, the resin is converted back to the hydrogen form (regenerated) by contact with a strong acid solution, or the resin can be conveded to the sodium form with a sodium chloride solution. For the above reaction, hydrochloric acid (HCl) regeneration would result in a concentrated nickel chloride (NiCl₂) solution.

(b) Weak Acid Cation Exchange Resins

These resins behave similarly to weak organic acids that are weakly dissociated. In a weak acid resin the ionizable group is a carboxylic acid (COOH) as opposed to the sulfonic acid group (SO₃H) used in strong acid resins. The degree of dissociation of a weak acid resin is strongly influenced by the solution pH. Consequently, resin capacity depends in part on the solution pH. A typical weak acid resin has limited capacity below a pH of 6.0, making it unsuitable for deionizing acidic metal finishing wastewater.

2. Anion Exchange Resins

These are those resins whose exchangeable ions are negatively charged. These are prepared by first chloromethylating the benzene rings of styrene-divinyl benzene copolymer to attach CH₂Cl groups and then causing these to react with tertiary amines such as triethylamine. The mechanism of anion exchange process can be represented by the following reaction:

\[
\text{Resin}^+ - \text{ex}^- + \text{A}^- \rightarrow \text{Resin}^+ \text{A}^- + \text{ex}^-
\]

Where, Resin+ indicates a polymer with N+ sites available for bonding with exchangeable anion (ex-), and A- indicates Cation in the surrounding solution getting exchanged.

Strong Base Anion Exchange Resins

Like strong acid resins, strong base resins are highly ionized and can be used over the entire pH range. These resins are used in the hydroxide (OH) form for water deionization. They will react with anions in solution and can convert an acid solution to pure water:

\[
\text{R-NH}_3\text{OH} + \text{HCl} \rightarrow \text{R-NH}_3\text{Cl} + \text{HOH}
\]

Regeneration with concentrated sodium hydroxide (NaOH) converts the exhausted resin to the OH form.

METHOD OF IER-DRUG COMPLEX FORMATION

Ion exchange resins may be supplied in case of cation exchangers as sodium, potassium or ammonium salts and of anion exchangers usually as the chloride. It is frequently necessary to convert a resin completely from one ionic form to another.

Charged drugs are normally loaded on to ion exchange resins by two methods,

i. Column method

ii. Batch method.
Column method
In this method a highly concentrated drug solution is passed through a column of resin particles. Since the reaction is an equilibrium phenomenon, maximum potency and efficiency is best obtained by the column method.

Batch method
In this method the drug solution is agitated with a quantity of resin particles until equilibrium is established. The reaction involved during complexation of drug with resin maybe indicated as follows

\[
\text{Re-COO-H}^+ + \text{Basic drug}^+ \rightarrow \text{Re-COO- Drug}^+ + \text{H}^+
\]

\[
\text{Re-N (CH}_3\text{)}^+3\text{Cl}^- + \text{Acidic drug}^- \rightarrow \text{Re-N (CH}_3\text{)}^+3\text{Drug}^- + \text{Cl}^-
\]

Upon ingestion, drugs are most likely eluted from cation exchange resins by H+, Na+ or K+ ions and from anion exchange resins by Cl\(^-\), as these ions are most plentiful available in gastrointestinal secretions.

Typical reactions involved in the gastrointestinal fluids may be envisaged as follows in the stomach:

\[
\text{Re-COO}^- \text{Drug}^+ + \text{HCl} \rightarrow \text{Re-COOH} + \text{Drug Hydrochloride}
\]

\[
\text{Re-N (CH}_3\text{)}^+3\text{Drug}^- + \text{HCl} \rightarrow \text{Re-N(CH}_3\text{)}^+3\text{Cl}^- + \text{Acidic drug}
\]

In the intestine:

\[
\text{Re-COO}^- \text{Drug}^+ + \text{NaCl} \rightarrow \text{Re-COONa} + \text{Drug Hydrochloride}
\]

\[
\text{Re-N (CH}_3\text{)}^+3\text{Drug}^- + \text{NaCl} \rightarrow \text{Re-N(CH}_3\text{)}^+3\text{Cl}^- + \text{Sodium salt of drug}
\]

**SELECTION OF SUITABLE ION EXCHANGE RESIN:**

The selection of IER for drug delivery applications is primarily governed by the functional-group properties of the IER [12]. However, the following points need to be considered during selection:

i. Capacity of the IER [i.e. the concentration of the exchangeable group in the resin, usually expressed in mill equivalents per gram (meq g\(^-1\)) of dry resin

ii. Degree of cross linking in the resin matrix

iii. Particle size of resin

iv. Nature of drug and site of drug delivery. It is also important to evaluate the resin in the pH- and ionic-strength environment, simulating the *in vivo* situation

v. Swelling ratio

vi. Biocompatibility and biodegradability

vii. Regulatory status of the IER.

For example, a low degree of cross linking of the resin will facilitate the exchange of large ions, but it will also cause volume changes in the resin upon conversion from one form to another. Similarly, the use of a strong IER will give a rapid rate of exchange, but it could also cause hydrolysis of the labile drugs because strong IER are effective acid-base catalysts. Therefore, a fine balance of all the parameters needs to be made to achieve optimal performance of drug-delivery systems (DDSs) containing IER.
PROPERTIES OF ION EXCHANGE RESINS

a. Particle size
Decreasing the size of the resin particles significantly decreases the time required for the reaction to reach equilibrium with the surrounding medium; hence larger particle size affords a slower release pattern.

b. Porosity
The limiting size of the ions, which can penetrate into a resin matrix, depends strongly on the porosity. The porosity depends upon the amount of cross-linking substance used in polymerization method [13]. The amount of swelling is directly proportional to the number of hydrophilic functional groups attached to the polymer matrix and is inversely proportional to the degree of DVB cross linking present in the resin.

c. Cross-linking
The percentage of cross-linking affects the physical structure of the resin particles. Resins with low degree of cross-linking can take up large quantity of water and swell into a structure that is soft and gelatinous. However, resins with high (Divinylbenzene) DVB content swell very little and are hard and brittle.

d. Exchange capacity
The exchange capacity refers to the number of ionic sites per unit weight or volume (mEq. Per gram or meq per ml). The weight basis values (mEq. per gm) is much higher than the volume based exchange capacity since the wet resin is highly hydrated. The exchange may limit the amount of drug that may be adsorbed on a resin, hence affect potency of the complex. Carboxylic acid resins derived from acrylic acid polymers have higher exchange capacities (10meq. /gm) than sulfonic acid (about 4meq. / gm) or amine resins because of bulkier ionic substituents and the polystyrene matrix. Therefore, higher drug percentages may often be achieved with carboxylic acid resins[14].

e. Acid base strength
It depends on various ionogenic groups incorporated into resins. Resins containing sulphonic, phosphonic or carboxylic acid exchange groups have approximate pKa values of <1, 2,3 and 4-6 respectively[15]. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having pKa values of >13, 7-9 or 5-9 respectively. The pKa values of resin will have significant influence on the rate at which the drug will be released in the gastric fluid.

f. Selectivity of resin for counter ion
Since IER involves electrostatic forces, selectivity mainly depends on relative charge and ionic radius of hydrated ions competing for an exchange site and to some extent on hydrophobicity of competitor ion.

g. Stability
The drug resinate is frequently more stable than the original drug. This is exemplified by the stabilization of vitamin B12 in the oldest pharmaceutical resinate application. Vitamin B12 has a shelf life of only a few months, but the resinate is stable for > 2 years. This technology is still used commercially today, more than 40 years after it was first introduced. Another example is nicotine. Nicotine discolors quickly on exposure to air and light but the resinate (used in nicotine chewing gums and lozenges) is much more stable.
h. Poor Dissolution

Many of today’s drugs are poorly soluble due to slow dissolution and/or low solubility. The rate of release of a poorly soluble, ionizable drugs from a resinate can be much quicker than the rate of dissolution of the pure drug. An excellent example is that of indomethacin which is only soluble up to ca 6ppm in simulated gastric fluid, but is released very quickly from a resinate. Using micronization to increase the rate of dissolution can be problematic, frequently requiring specialized equipment, and often having problem with agglomeration of the fine particles after grinding. The grinding can also result in melting and conversion to other crystal forms (see below). These problems are completely eliminated by using the ion exchange resin approach.

i. Deliquescence

Deliquescence is the property of a solid whereby it absorbs so much water that it dissolves in the water it absorbs. While this is not a common problem it has been a very difficult one to solve, and requires the use of specialized equipment or careful scheduling of production in dry seasons. However, the resinate of a deliquescent drug is not deliquescent, permitting its formulation into typical dosage forms in standard equipment. Even under severe conditions the resinates remain solid. In fact, the amount of water absorbed decreases with increased amount of valproate in the resin. Under typical ambient conditions the resin remains free-flowing even if water is absorbed.

j. Polymorphism

Unlike deliquescence, polymorphism is a very common problem in the pharmaceutical industry and huge sums of money are spent trying to identify polymorphs and trying to make stable, suitably soluble forms. Failure to resolve such problems can result in significant stability problems for the final dosage form. Ion exchange resins present a unique way to deal with the problem. A drug resinate is an amorphous solid that cannot crystallize or even form hydrates. In addition the release of the drug from the resinate is independent of the crystal form that was used to make it. Consequently, using resinates completely eliminates any problems with polymorphism.

k. Physical State

While most drug substances are solids there are some that are liquids or difficult-to-handle solids. Because the physical properties of the resinates are similar to the resin not the drug, the resinates of these troublesome drugs will be free-flowing solids. A very well established example of this is the nicotine resinate used in nicotine chewing gums and lozenges. Nicotine is a liquid, but the resinate is a stable, free-flowing solid.

l. Tablet Disintegration

Certain of the ion exchange resins swell significantly on exposure to water. This has led to their use as very effective tablet disintegrants. It is usually necessary to use only a few percent of the tablet weight to get complete disintegration within several minutes.

m. Taste

Because resinates are insoluble in water they have no taste. This makes them excellent candidates for taste-masking foul tasting drugs. As long as the rate of release of the drug on contact with saliva is sufficiently slow (and it frequently is) this technology works extremely well. It is equally applicable to liquid formulations (suspensions) and dissolve-in-the-mouth tablets. It is particularly effective in liquid formulations because the resinate will represent the thermodynamically stable form so that leaching of the drug into the aqueous phase will not occur. There are several examples of the use of this technology in the market place including a liquid form of paroxetine.
n. Extended Release

One of the early applications of ion exchange resins in drug formulation is their use in extended release. The first commercial example of this was known as the PennKinetic system where dextromethorphan was loaded onto a resin and the resin was then coated. This combination gave an extended release liquid formulation that is still sold commercially (Delsym®). The technique, but without the coating, has also been used for many years for extended release diclofenac. Until recently this technology was limited by the release profile. While the overall release rate could be changed, the shape of the release profile was always the same - a typical first order release. However recent innovations have identified ways to change this shape significantly, even to the point of achieving almost constant release rate.

o. Multiple Benefits

The benefits described are not necessarily mutually exclusive to one another. One example is the nicotine chewing gum. Here the main reason for making the nicotine resinate (nicotine polacrilex USP) is to extend the release of the nicotine from the chewing gum so that it last 10-20 minutes. However the resinate also increases the stability of nicotine and makes it into an easily formulated, less toxic solid. Another example is in Delsym® where the main reason for the resinate/coating is to create an extended release suspension. However, it also provides excellent taste-masking.

CONCLUSION

From the foregoing discussion it is clearly evident that taste masking of drug by ion exchange resin is economical, simple and convenient method having enormous potential. A wide variety of techniques are used in order to mask the bitter taste of the drug. Still one of the most economical methods for taste masking is the use of ion exchange resin. Ion exchange resins have been used in pharmacy and medicine for various functions, which include tablet disintegration, bioadhesive systems, sustained release systems. The use of IER in drug delivery research is gaining importance and commercial success. In addition to oral drug delivery, IER systems are being explored for site-specific, transdermal, nasal and ophthalmic Routes. Moreover, several novel concepts, such as sigmoidal release, floating, pH and ionic strength-responsive systems, have shown the potential use of IER in drug delivery.

REFERENCES