ION EXCHANGE RESIN AS AN IMPOSING METHOD FOR TASTE MASKING: A REVIEW

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ABSTRACT

Taste masking becomes a pre-requisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. 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. The field of taste masking of active pharmaceutical ingredients (API) has been continuously evolving with varied technologies and new excipients. This review highlights complete account of ion exchange resin and its application in taste masking of bitter drugs.

Keywords: Ion exchange resin, taste masking, bitter drug.

INTRODUCTION

The word ‘medicine’ for a child is synonymous with bad taste. Taste can be separated into five primary taste qualities: sweet, sour, salty, bitter, and umami or savory. Within hours after birth, infants reject bitter tastes and prefer sweet and umami tastes\(^[1]\). Children have a much greater number of taste buds than adults which are responsible for sensitivity toward taste. These taste buds regenerate every two weeks. As with many of the senses, taste becomes altered as a function of the aging process, which explains why most children find certain flavors to be too 'strong' when adults do not.

The American Academy of Pediatrics estimates that compliance in children is as low as 53%, indicating that children frequently fail to take medications properly. Non-compliance can lead to: Persistent symptoms, Need for additional doctor visits or even hospitalizations, Worsening of condition, Need for additional medications, Increased healthcare costs and Development of drug-resistant organisms in cases of infectious diseases\(^[2]\).
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[3]. 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[4]. 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[5].

Factors affecting selection of taste masking technology

Different taste masking technologies have been used to address the problem of patient compliance[6]. 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[7]. 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[8]. 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

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\[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. Detail of IERs are available which are summarized in Table - 1.
### TABLE 1: EXAMPLES OF IER – DRUG COMPLEX

<table>
<thead>
<tr>
<th>Resin Name</th>
<th>Functionality</th>
<th>Polymer backbone</th>
<th>Medicament</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberlite™ IRP64</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Dextromethorphan, Dimenhydrinate</td>
</tr>
<tr>
<td>Amberlite™ IRP69</td>
<td>Strong acid SO³⁻</td>
<td>Styrene-Divinyl Benzene</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Amberlite™ IRP88</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Talampacillin-HCl, Paroxetine</td>
</tr>
<tr>
<td>Indion 204</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Norfloxacin, Ofloxacin</td>
</tr>
<tr>
<td>Indion 214</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Indion 234</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Ciprofloxacin, Chloroquin phosphate</td>
</tr>
<tr>
<td>Kyron T-104</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Cefpodoxime proxetil</td>
</tr>
<tr>
<td>Kyron T-114</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>Kyron T-134</td>
<td>Weak acid COO⁻</td>
<td>Crosslinked polyacrylic</td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>

**Properties of IER**

**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\textsuperscript{[12]}. 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\textsuperscript{[13]}.

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\textsuperscript{[14]}. 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.
Desired properties of pharmaceutical grade IERs

a) Fine, free flowing powders  
b) Particle size of  25 - 150 microns  
c) Contain functional group that capable of exchanging ions and/or ionic groups  
d) Insoluble in all solvents, all pH’s  
e) Not absorbed by body  
f) Do not have a defined molecular weight  

CONCLUSION

IERs is presently one of the most exciting technologies for the paediatric industry, being an ideal process where the taste of bitter medicament can be masked successfully. IERs have been used in pharmacy and medicine for various functions, which include tablet disintegration, bioadhesive systems, sustained release systems. In recent years IER have been successfully utilized for masking of taste of bitter drugs.

REFERENCES


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