

**ION EXCHANGE RESIN AS A POTENTIAL TECHNOLOGY ON FOR TASTE MASKING: A REVIEW**Rupa Gupta*, P.K Sharma¹, Ashish Arora², Rishabha malviya¹¹Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida, U.P., India²Senior scientist, Ranbaxy, R&D (Product development & Research), Gurgaon, India***Corresponding author e-mail:** rupa.gupta.sep16@gmail.com**ABSTRACT**

Taste masking is a gold standard technology to mask the unpleasant taste of bitter active pharmaceutical ingredient. Therefore, it becomes a potential tool to improve the patient compliance & drug bioavailability. Taste masking of bitter drug using Ion exchange resin (IER) is one of the popular approaches. Ion exchange resin are cross-linked synthetic high molecular weight insoluble organic polymer having ionizable functional group. As being high molecular weight, the resin are not absorbed by the body & are therefore inert. In past few years, Ion exchange resin have since been extensively used in the drug delivery technologies included; site specific drug delivery system, Modified release dosage form, Fast dissolving tablet, clinical medicine & Biomedical application etc. The purpose of writing this review to explore the importance & application of Ion exchange resin because of their versatile properties as a taste masking technologies.

Keywords: IER, Taste masking & Technologies, Bitter drug, Resin drug complex.**INTRODUCTION**

Taste masking is defined as the apparent reduction of an unpleasant taste by using suitable agent. Taste masking technologies are very important approach for improving patient compliance & better therapeutic efficacy. Many oral drug delivery formulations have objectionable taste such as bitterness, saltiness or sourness. Taste masking involve in eliminating or preventing directly interaction of bitter drug & inhibit the production of negative sensory response & thereby it improve the ease of administration of taste masked dosage form followed by patient compliance. Taste masking using IER is one of the most effective & efficient approaches for the taste masking of an unpleasant taste of bitter drug. The aim and objective of writing of this review is to apart from traditional application of separation, purification and processing, ion exchange resin are being researched for their pharmaceutical applicability. Be it taste masking, modified release or sustained release, dissolution

enhancement or as a potential disintegrating agent ion exchange resin have proven their worth in the pharmaceutical industries. Ion exchange resins can be used to overcome various pharmaceutical formulation problems including bitter taste, poor stability, deliquescence, and poor dissolution of the drugs. Resins have also been used as Superdisintegrant in tablet formulations because of their swelling properties.

IER is defined as “Ion exchange resin are cross-linked synthetic high molecular weight solid water insoluble usually white or yellowish, fabricated from organic polymer (polyelectrolyte) having ionizable functional group¹. The principle of IER at which it act is that it is an reversible process that exchange their mobile ion of equal charge with the surrounding insoluble organic polymer having charged functional site². The drug release from the resins is by exchanging with ion in the gastrointestinal fluid followed by drug diffusion³. As IER itself being a high molecular weight, the resin are not absorbed by

the body & are therefore inert. The trapping of ions takes place only with simultaneous release of other ions; thus, the process is called ion exchange⁴.

To impart the taste masking of bitter drug weak cation exchange resin or weak anion exchange resin are used where it is depend upon the nature of the drug used for the same. The nature of the drug resin complex formed is s that of average pH of 6.7& cation concentration of about 40 meq/l in the saliva are not able to break the drug resin complex but it is enough to break the drug resin complex by HCL in the stomach & therefore drug resin complex is tasteless with no after taste & at the same extent of time, its bioavailability should not be affected.

PRE-REQUISITE OBJECTIVE OF THE TASTE MASKING:

There are following parameter which is pre-requisite during the taste masking⁵.

- Reduction of solubility of drug in the saliva along with without affecting its bioavailability and solubility.
- Require excipients that are economical and easily available.
- Least manufacturing cost.
- To inhibit the directly interaction of bitter drug to the taste bud receptor.
- Ease to administration & Patient compliance should be improved specially in geriatric & pediatric patient without getting affecting drug bioavailability.

REQUIRED CHARACTERSTICS PARAMETERS OF PHARMACEUTICALLY USED ION EXCHANGE RESIN:

While using the IER for the taste masking should have following Characteristics such as :⁶

- IER should not absorbed by the body i.e. it should be inert.
- Particle size should be within the range of 25-150 micron.
- IER should have uniform, fine & free flowing properties.
- IER should containing functional groups which exchange their mobile ions.
- IER should be insoluble at all pH & saliva.
- Biocompatibility & biodegradability.
- Swelling ratio of IER.

IDEAL ABILITY OF ION EXCHANGE RESIN:

To prevent the possible parameter which may affect the formulation IER should having following idealability included:

1-EXCHANGE CAPACITY:

The exchange capacity is defined as the “Number of ionic sites per unit weight or volume (mEq. Per gram or meq per ml).The exchange capacity of IER in weight basis having higher value than the volume based capacity value. Therefore, the wet resin is highly hydrolyzed. Carboxylic acid resins are derivatives of acrylic acid polymers with higher exchange capacities about (10meq. /gm) than sulfonic acid (4meq. / gm) or amine resins because of their bulky ionic substituent’s & the polystyrene matrix. Hence, It is concluded that higher drug percentages can be grab with carboxylic acid resins⁷.

2-pH : pH is an important factor that play an important role in taste masking and it affects the drug complexation efficiency & drug release from resin complex. As dissociation increases as well as complexation efficiency get improved. Whenever, pH of surrounding medium is acidic then it dissociation of basic drugs occur resulting formation of more ionic species available for drug loading. And , towards alkaline pH, the dissociation of acidic drugs will be promoted⁸.

3-STABILITY : At inherent condition like Humidity, Light, Temperature, Oxygen etc; the resin has been found to be stable & inert in nature^{9,10}.

4-PARTICLE SIZE OR SIZE OF EXCHANGE:

The smaller resin beads promotes more surface area leads to rapid exchange of ion but significantly decreases the time required for the reaction to achieve equilibrium with surrounding medium. Hence, larger beads size having more diffusional path length affords sustain release pattern¹¹.

5-TOXICITY:

As resin are polymerized form & not absorbed by the body, so as to its nature are inert. There are purification process is to be needed prior to usance of resin in drug formulation to avoid possible toxicity¹².

6-pka :

The pka value of the resin play an importance role on the drug release from the resinsates in to gastric fluid & also having role in the extent of dissociation & complexation with the resin. The anionic resin having sulfonic, phosphonic or carboxylic acid exchange groups with nearly pka value of <1-6.While cationic resins containing quaternary, tertiary, or secondary ammonium groups have pKa values of 5-13 and greater than 13.¹³.

7-INFLUENCE OF TEMPERATURE :

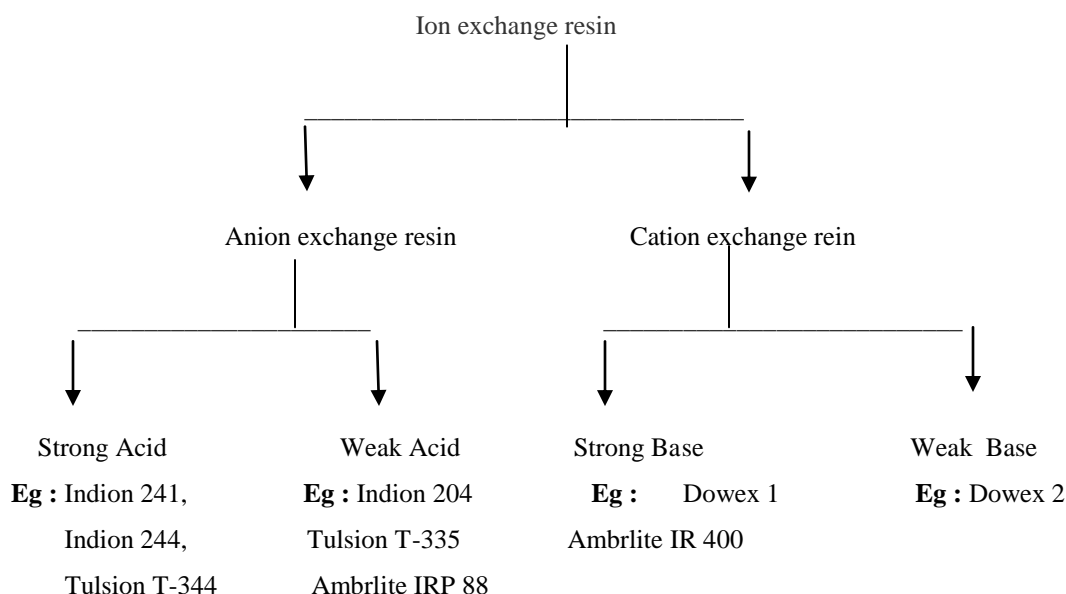
cation exchange resin doesn't get significantly influenced by temperature changes unlike while anion exchangers get affected at high temperature & may leads to swelling of resin. Hence, drug loading capacity of certain resin may affected by changing in temperature.¹⁴.

8-SELECTIVITY OF COUNTER ION :

It is highly depends on both the relative charge & radius of hydrated ions competing for exchange site. The cationic drug replaced those ion that have low selectivity for resin such as $-H^+$ higher loading^{15,16}.

TYPE OF ION EXCHANGE RESIN :

Based on the charge of the functional groups present, ion exchange resins are classified into cation exchange resins and anion exchange resins. With in each category, they are classified into strong and weak depending on their affinity for counter ions. Cation exchange resins are exchangers of sodium, potassium or aluminium salts and anionic resins are for chloride ions. Ion exchange resin are classified as:¹⁷



MECHANISM OF ION EXCHANGE RESIN COMPLEXATION FOR TASTE MASKING OF BITTER DRUG:

Ion exchange resin is solid & insoluble high molecular weight polyelectrolyte's that can exchange their mobile ion of equal charges with the surrounding medium reversibly. Ionized drug & drug exchanger form a stable complex for the short period of exposure to making the drug unavailable for taste sensation i.e. Taste masking.

The mechanism of binding of drug to the IER involves the electrostatic interaction between resin & oppositely charges drug & also the hydrophobic interaction. Drug released from the ion exchange in to the surrounding media is due to the following reason included:

- Low pH in the stomach
- Increasing ionic concentration in the GIT
- Larger volume of the surrounding media

- Increasing gastric residence time & is thus, available for absorption.

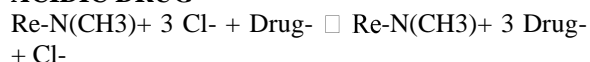
The drugs are loaded on to the resins by column method and batch method.^{18,19}

COLUMN METHOD : Highly concentrated drug solution is passed through the column containing resins. Maximum efficiency is best obtained by the column method.

BATCH METHOD: In this method the drug solution is agitated with a quantity of resin until equilibrium is attained.

REACTION INVOLVED IN COMPLEXATION OF DRUG WITH RESIN:

ACIDIC DRUG-



BASIC DRUG-

$$\text{Re-COO-H}^+ + \text{Drug}^+ \rightleftharpoons \text{Re-COO- Drug}^+ + \text{H}^+$$
TYPICAL REACTION INVOLVED IN GASTROINTESTINAL FLUIDS:**ACIDIC DRUG-**

$$\text{IN STOMACH: Re-N(CH}_3\text{)}_3 + 3 \text{ Drug}^- + \text{HCl} \rightleftharpoons \text{Re-N(CH}_3\text{)}_3 \text{ Cl} + \text{Drug}^- \text{ (Free form)}$$

$$\text{IN INTESTINE: Re-N(CH}_3\text{)}_3 + 3 \text{ Drug}^- + \text{NaCl} \rightleftharpoons \text{Re-N(CH}_3\text{)}_3 \text{ Cl} + \text{Drug}^- \text{ (Sodium salt)}$$
BASIC DRUG-

$$\text{IN STOMACH: Re-COO- Drug}^+ + \text{HCl} \rightleftharpoons \text{Re-COOH} + \text{Drug}^- \text{ HCl}$$

$$\text{IN INTESTINE- Re-COO- Drug}^+ + \text{NaCl} \rightleftharpoons \text{Re-COONa} + \text{Drug}^- \text{ HCl}$$

In taste masking by ion exchange resins, the resin drug complexes formed will elute only a limited % of drug in the saliva pH. Thus the taste of the drug is masked without interrupting the drug release profile (as shown in above reactions).

APPLICATION OF ION EXCHANGE RESIN :

Because of the versatile utility of IER & its potential benefits, they are highly used for various drug delivery & therapeutic application included :

1-TASTE MASKING: Taste masking to improve patient compliance. 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. Example of taste masking of some drugs using Ion exchange resin such as:^{20,21,22,23}

TABLE 1: Example of taste masking of some drugs using Ion exchange resin

S. No.	Drug	Dosage form	Resin Used
1.	Paroxetin hydrochloride	Liquid suspension	Amberlite IRP88
2.	Ranitidine Hydrochloride	Chewable Tablet	Amberlite IRP69/88
3.	Remacemide hydrochloride	Dry / liquid suspension	Amberlite IRP64
4.	Erythromycin,	Liquid suspension	Carbomer 934
5.	Orbifloxacin	Dry / liquid suspension	Amberlite IRP64/69
6.	Dextromethorphan hydrobromide	Dry / liquid suspension	Carbomer 934

2-DRUG STABILIZATION: eg- To improve the stability of vitamin B₁₂ using weak acid cation exchange resin (Indion 264)²⁴.

3- AS A DISINTEGRANTES/ SUPER DISINTEGRANTE : Pollacrilline a potassium salt of weakly acidic cation exchange resin with methacrylic acid divinyl benzene matrix. Are used as a tablet disintegrantes²⁵.

4-HIGH PURITY WATER : For the water softening uses a cation exchange resin to exchange principally calcium and magnesium ions for sodium ions and so prevent the formation of calcium carbonate precipitates on Reverse Osmosis membranes²⁶.

5- ENHANCEMENT OF DISSOLUTION : Drug resin complex transform drug to amorphous form. Therefore, drugs having poor solubility, during the

process of desorption, drug are immediately release resulting improved drug dissolution²⁷.

6- POWDER PROCESSING: As the structure of resin possesses a rigid structure so that handling processing of hygroscopic drug get improved & also avoid the caking problem²⁸.

7- APPLICATION IN VARIOUS DRUG DELIVERY: Ion exchange resin are also used in various drug delivery system such as :

- Oral modified release drug delivery formulation included:^{29,30}
 - Microencapsulated or coated resenates.
 - Simple resenates & Hollow fibre system.
- Fast dissolving tablet formulation
- Site-specific drug delivery formulation included as :^{31,32,33,34}
 - Gastric retentive system.

- For cancer treatment.
 - Sigmoidal release systems.
 - Nasal drug delivery.
 - Ophthalmic drug delivery.
 - Iontophoretically assisted transdermal drug delivery.
- Therapeutic application : It included as following :^{35,36}
- Cholesterol reducer
 - Chewing gum for glycol absorption
- Regulation of Ion exchange resin for the water, food & Beverage industries³⁷.
- Clinical application of Ion exchange resin : It has following application such as :³⁸
- It is highly used as to improve the low sodium diet
 - Hemoperfusion
 - in the treatment of type II hyperlipoproteinemia and familial hyperlipoproteinemia in children and young adults. eg-cholestyramine and cholestipol (Anion exchange resin)

CONCLUSION

Taste masking of the drug employing ion exchange resins (IER) has proved to be safe and effective method for formulation of various dosage forms. Administration of a oral drug with bitter taste and acceptable level of palatability has always been a in developing a formulation for pediatric and geriatric purpose. Taste masking using Ion exchange resin has therefore become a potential tool to improve patient compliance. It has a broader application in various field.

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