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ION EXCHANGE RESIN COMPLEXATION TECHNIQUE FOR PHARMACEUTICAL TASTE MASKING: AN OVERVIEW

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ABSTRACT

Ion exchange resins have gained immense significance in the recent years owing to their multiple benefits as drug delivery vehicles. Taste masking of bitter tasting drugs have emerged as one of the major application of ion exchange resins in pharmaceutical product development. The major highlight of ion exchange resin complexation is the retarded release of drug in saliva and complete release from the complex in gastric environment. Thus taste masking of bitter drug is achieved without affecting its intrinsic bioavailability. Ion exchange resins are polymers that contain appropriately substituted acidic groups, such as carboxylic and sulfonic for cation exchangers; or basic groups, such as quaternary ammonium group for anion exchangers. In the present review, the technique of ion exchange resin complexation has been presented as a viable technique for taste masking of bitter pharmaceuticals to improve patient compliance. The manuscript highlights the different types of ion exchange resins employed for complexation, its mechanism and application in pharmaceutical taste masking. The methods for preparation of ion exchange resinate and factors affecting the complexation are also briefly discussed in the present article.

KEYWORDS: taste masking; resinates; ion exchange resins; complexation; bitter drugs.

INTRODUCTION

The majority of newly developed drug are designed for oral application since they can be self-administered by the patient.[1] Oral dosage forms are designed according to the nature of the drug, the nature of application and the need for any special effects. The common oral dosage forms include: liquid mixtures like solutions, suspensions, solid dosage forms like tablets and capsules and liquid filled capsules etc. A central challenge of administering

medicine for oral use to children is bitter taste. The bitter taste of medicament has emerged as the biggest obstacle in their oral administration thereby affecting the patient compliance.[2] The bitter taste either during or immediately after oral administration often hampers the performance of drug for oral delivery which results in poor compliance especially in case of pediatric and geriatric medications.[3] The poor compliance result in discontinuities in therapy causing a lot of revenue loss to pharmaceutical companies.[4-5]

Taste masking of bitter drugs is now on the top most priority of pharmaceutical companies in order to improve upon the various problems arising out of poor taste and palatability.[6] Various techniques based on different principles have been investigated and described in academic and patent literature for masking of bitter or undesirable taste of drugs like addition of flavors, sweetener and amino acids, microencapsulation, inclusion complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach.[7-10] Ion exchange resin complexation has emerged as a simple, efficient and viable technique for taste masking of a number of bitter tasting drugs.

Ion exchange resins comprises of insoluble polymers that contain acidic or basic functional groups with an ability to exchange counter-ions within aqueous solutions surrounding them. In the present article, the technique of ion exchange resin complexation and its application in pharmaceutical taste masking has been reviewed. The present article also briefly discuss the ion exchange resins employed for taste masking of drugs and the factors affecting ion exchange resin complexation.

ION EXCHANGE RESIN COMPLEXATION

Complexation with ion exchange resin is a simple, efficient and proven technique for taste masking of a number of bitter drugs.[11-12] The basic mechanism involved in this technique is the attachment of bitter drugs to oppositely charged resin substrate resulting in formation of drug resinate. The salivary environment with an average pH of 6.8 and a cation concentration of 40 meq/L does not allow the drug to be disassociated from the resin complex.[13] This primarily is the reason for masking of unpleasant taste of bitter drugs. Immediately after the drug reaches the gastric environment, it is broken down due to large concentration of hydrogen ions. The hydrogen ions in the stomach displaces the drug from the complex and cause rapid elution from or disintegration of ion exchange resin drug complex and release the drug in the gastric content. The free drug is now bioavailable, which can be easily absorbed

from the gastro intestinal tract. Thus, taste masking of a drug is achieved without affecting the release of drug.[14]

ION EXCHANGE RESINS

Ion exchange resins (IER) are high molecular weight insoluble polymers containing loosely held ions which have the ability to exchange other ions in solutions which come in contact with them. Chemically ion exchangers are insoluble acids or bases which have insoluble salts enabling them to exchange positively charged ions (cation exchangers) or negatively charged ones (anion exchangers). The presence of ionic site in a drugs molecule provides a means to loosely attach such drugs to insoluble charged resins.[15] Ion exchange resins are generally classified as cation exchangers and anion exchangers, which is based on the type of ions to be exchanged. Cation exchangers have positively charged mobile ions and anion exchangers negatively charged exchangeable ions. The ionizable group attached to the hydrocarbon network of resin structure determines the chemical behavior of the resin. Resins can be broadly classified as strong or weak acid cation exchangers or strong or weak base anion exchangers. In general, an ion exchange process takes place by replacement of dissimilar and displaceable ions of the same charge contained in the ion exchange resin.[16]

Strong acid cation exchange resins

Principal sulfonated styrene-divinylbenzene copolymers are employed as strong acid cation exchange resins. These are spherical resins prepared by the sulfonation of styrene-divinylbenzene copolymer beads with sulfonating agents of choice: sulfuric acid, chlorosulfonic acid, or sulfur trioxide. The taste and odor of cationic drugs (amine containing) prior to their formulation into suitable dosage form can be masked by these resins.[17]

Weak acid cation exchange resin

Cross linking an unsaturated carboxylic acid such as methacrylic acid with a cross linking agent such as divinyl benzene results in preparation of these resins. These resin function above pH 6.[17] These types of ion exchange resins are used for taste masking of bitter drugs containg –COOH functional group. Weak cation exchange resins are the most commonly used resins for taste masking of pharmaceuticals

Strong base anion exchange resins

These are quaternized amine resins prepared by the reaction of triethylamine with chloromethylated copolymer of styrene and divinylbenzene. Apart from pharmaceutical taste masking, these types of resins also found application in deionization of water and in pharmaceutical analysis as a separation media for thin layer chromatography. [17]

Weak base anion exchange resins

Primary and secondary amines or ammonia react with chloromethylated copolymer of styrene and divinylbenzene to form these resins. These weak base anion exchange resin function well below pH 7. These resins found application in chemical industry and in pharmaceutical analysis.[17]

Table 1 provides a list of commercial resins which are currently being used for taste masking by ion exchange resin complexation.

MECHANISM OF COMPLEXATION

The ion exchange phenomenon is based on electrostatic interactions between the resins and ionizable drugs. The electronic difference between the ions is the driving force behind this exchange. The reversibility of this interaction is exploited in oral drug delivery in which the resins may carry the drug and passes as tasteless in salivary environment and release the drug in a certain region of the GIT due to presence of competing ion in gastric fluid.[18] Following is a depiction of reaction involved during complexation of drug with resin.

$$Re\text{-}N\,(CH_3)_3{}^{+}Cl^{-} + \text{Acidic Drug}^{-} \Leftrightarrow Re\text{-}N\,(CH_3)_3{}^{+}\,\text{Drug}^{-} + Cl^{-} \quad \text{---- Eqn. 1}$$

$$Re\text{-}COO^{-}H^{+} + \text{Basic Drug}^{+} \Leftrightarrow Re\text{-}COO^{-}\,\text{Drug}^{+} + H^{+} \quad \text{---- Eqn. 2}$$

Reaction involved in gastrointestinal fluid with resonates.

In gastrointestinal fluid, the drug is eluted from cation exchange resin by H^+, Na^+ or K^+ ions and by Cl^- from anion exchange resin, as these ions available in large concentration in gastrointestinal secretions.

In the stomach

$$Re\text{-}COO^{-}\,\text{Drug}^{+} + HCl \Leftrightarrow \text{Drug Hydrochloride} + Re\text{-}COOH \quad \text{---- Eqn. 3}$$

$$Re\text{-}N\,(CH_3)_3{}^{+}\,\text{Drug}^{-} + HCl \Leftrightarrow Re\text{-}N\,(CH_3)_3\,Cl + \text{Acidic Drug} \quad \text{---- Eqn. 4}$$

In the intestine

$Re\text{-}COO^{-}\ Drug^{+} + NaCl \Leftrightarrow$ Drug Hydrochloride + Re-COONa ---- Eqn. 5

$Re\text{-}N\ (CH_3)_3^{+}\ Drug^{-} + NaCl \Leftrightarrow Re\text{-}N\ (CH_3)_3\ Cl$ ---- Eqn. 6

PREPARATION OF RESINATE

Two methods namely batch process and column process is employed for preparation of drug resinates. The highlights of these two methods are as follows.

Batch Process

In this process, an ion exchange resin is added to water in order to prepare its slurry. The accurately weighed amount of drug is then added to this slurry which is followed by stirring to prepare the complex. After the formation of complex, it is washed with water and dried [19]. Mixing time of drug and resin, pH, temperature and swelling of resin and drug: resin ratio is several factors, which can affect the complexation of the drug with resin.[20]

Column process

In a typical column procedure the resin is slurried in water and added to a column and backwashed with water to eliminate air pockets and distribute the beads. Acid (0.1N HCl) is added to convert the acid cycle, followed by washing with water. The cake is then removed from the column, subjected to vacuum filtration and finally dried in an oven. An analogous procedure can be used to absorb a carboxylated drug on ion exchange resin, using NaOH to convert the resin to basic cycle.[19]

The batch process is always preferred over column process in case of preparation of taste masked ion exchange resinates. The major reason behind this is the fine particle size of the ion exchange resins which does not allow them to be used in columnar operations due to chances of washing away during operations. Higher swelling efficiency in the batch process makes more surface area available for ion exchange.[20]

FACTORS AFFECTING ION EXCHANGE RESIN COMPLEXATION

Following are the various factors that affect the process of ion exchange resin complexation and thereby needs special considerations.

Particle size and form

The size of the resin particles affects the rate of ion exchange reaction. The reduction in size

of the resin particles results in decreased time required for the reaction to reach the equilibrium with the surrounding medium.[21]

Porosity and swelling

Porosity affects the ability of ions to penetrate into resin matrix and thus the efficiency of complexation. The amount of cross-linking substance used in polymerization method determines the porosity of resin. 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.[22]

Cross-linking

The cross-linking percentage affects the physical structure of the resin particles. Resins having low degree of cross-linking can take up large quantity of water and thus swell into a soft and gelatinous structure. Cross-linkage also affect the loading efficiency of resin by affecting its porosity and swelling properties.[22]

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 exchange capacity determines the amount of drug that can be adsorbed on a resin hence the potency of a complex.[21]

Mixing time

The increase in mixing time enhances the swelling of resin which ultimately results in increased drug loading. Lower mixing time results in improper swelling and decreased percentage of drug complexation.[21]

Effect of temperature

For certain resins the effect of temperature on drug loading has been reported. High temperature may also cause swelling of resin. Cation exchange resin doesn't get significantly affected by temperature changes unlike anion exchangers.[22]

pKa

The pKa value of the resin is having significant influence on the rate at which the drug is released from the resinate in the gastric fluids. The pKa of drug also decides the extent of dissociation and complexation with the resin. If the pH is higher than pKa of drug, the drug remains mostly in nonionized form resulting in decreased complexation. At a certain pH,

wherein, both the drug and the resin are ionized in sufficient quantity, resulted in maximum resinate formation.[21]

Stability

At ordinary temperature and environmental conditions, the ion exchange resins are inert substances and resistant to decomposition through chemical attack. They get degraded and degenerated in presence of gamma rays.[21]

Purity and toxicity

Resins are not absorbed by body tissue and are safe for human consumption Careful purification of resins is required to remove any toxic impurities. In a test conducted for toxicological tolerance, the resins were found to be physiologically inert and non toxic at recommended dosage.[22]

APPLICATION IN TASTE MASKING

Ion exchange resin complexation has found application in the taste masking of a number of bitter drugs as shown in Table 2.[23-34] Some of the major applications of ion exchange resin complexation in taste masking are discussed as follows.

Barodkin and Sundberg**,** prepared high potency adsorbates of methapyrilene, dextromethorphan, ephedrine, and pseudoephedrine by column procedures using a polymethacrylic acid ion-exchange resin. Taste evaluation of the adsorbates showed a significant reduction in bitterness of the drugs. Coating the adsorbate particles with a 4:1 ethylcellulose-hydroxypropylmethylcellulose mixture reduced the bitterness further. Taste coverage was maintained after incorporation of the coated adsorbate into chewable tablets.[35] Manek and Kamat, evaluated Indion CRP-244 and CRP-254 as sustained release and taste masking agents. Both the ion exchange resins were found to be very effective in the masking of bitter taste.[36] Lang *et al.*, developed the ion exchange resinates of known antibacterial quinolonecarboxylic acid derivatives such as ciprofloxacin using weak cation exchange substance. The taste was remarkably improved in the drug formulation was readily accepted.[37] Leonardo and Cooper, developed an oral liquid pharmaceutical composition comprising a paroxetine-Amberlite IRP88 complex. The molar ratio of Amberlite IRP 88 to paroxetine for complexation was 1:1 to 2:1.[38] Agarwal *et al.*, prepared high-potency adsorbates of chloroquine phosphate (CQP) by the batch method using a polyacrylic acid ion-exchange resin. Significant masking of the bitterness of the drug was shown in taste

evaluation of the adsorbates. The complex formation was complete at pH 6.0. The complex was found to be stable at all conditions for 1 month in a stability testing. Drug elution from the complex was found to be completed at pH 1.2 and 2.0 in an *in vitro* release study [39].

Pisal *et al*., formulated tasteless complexes of ciprofloxacin with Indion 234 and evaluated the molecular properties of drug complexes. The effect of batch and column process, complexation time, temperature, and pH on ciprofloxacin loading on Indion 234 was reported. Drug resin complexes (DRC) were characterized by infrared spectroscopy, thermal analysis, and x-ray diffraction pattern. Ciprofloxacin release from DRC was obtained at salivary and gastric pH and in the presence of electrolytes. The drug-resin ratio of 1:1.3 was found to be optimum to achieve efficient drug loading in batch process using activated Indion 234. Drug complexation was found to enhance with increase in pH from 1.2 to 6, while temperature was not found to affect the complexation. Infrared spectroscopy revealed complexation of -NH (drug) with Indion 234.[40] Patravale and Prabhu**,** developed taste-masked resinates of extremely bitter drug quinine sulphate using ion exchange resins. The drug resin complexation procedure was optimized with respect to parameters like drug to resin ratio, volume of medium and taste of the complex. The taste-masked complex was then formulated into a suspension dosage form. The suspension was evaluated for various quality control parameters. The suspension showed complete masking of the bitterness of the drug in a taste evaluation study. *In vitro* release studies revealed complete drug elution from the complex after a period of 30 min in pH 1.2 buffer.[41]

Zeng et al., utilized ion exchange resins (IERs) as carriers to develop a dual-drug taste masked sustained release suspension containing codeine, and chlorpheniramine. The codeine resinate and chlorpheniramine resinate beads were prepared by a batch process using amberlite IRP69 ion exchange resin and then impregnated with polyethylene glycol 4000 (PEG 4000). The PEG impregnated drug resinate beads were further coated with ethylcellulose by the Wurster process. The coated PEG impregnated drug resinate beads were dispersed in an aqueous suspending vehicle containing 0.5% w/w xanthan gum and 0.5% w/w of hydroxypropylmethylcellulose. The drug release study was performed in 0.05 M and 0.5M KCl solutions. The release of codeine from resinate beads was found to be more rapid than chlorpheniramine in the same ionic strength. Relative bioavailability and pharmacokinetics evaluation of the formulated suspension, in beagle dogs showed the longer value of T_{max} and the lower value of C_{max}, conforming the sustained release effect.[42]

Bhise *et al.*, masked the bitter taste of Diphenhydramine Hydrochloride (DPH) using Indion 234 and Tulsion 343 as cation exchange resins. The drug: resin ratios of 1:1, 1:2, and 1:3 were employed to prepare the drug resin complexes (DRC) by batch process. The optimum drug: resin ratio and the time required for maximum complexation was determined. The drug resinates were evaluated for different parameters such as drug content, taste, micromeritic properties drug release and X-ray diffraction (PXRD). The drug resinates were found to be successful in taste masking of DPH and the confirmation of complex formation was done by X-ray diffraction which revealed the monomolecularity of entrapped drug in the resin complex. The optimum drug:resin ratios of 1:2 and 1:1 was further formulated into effervescent and dispersible tablets. The developed formulations were found to have good uniformity of dispersion, disintegration time and 95% of drug released in 15 min from effervescent and dispersible tablets.[43] Shukla *et al.*, incorporated a tasteless complex of risperidone using ion exchange resin (IER) into orally disintegrating tablets (ODT). Resinate was found to be tasteless at salivary pH as only 2.5% of drug was released in 120 sec in 5 ml of pH 6.8 phosphate buffer. However, 92% of drug was released in 5 min from 0.1 N HCl dissolution media, indicating complete release of the drug from the complex in the stomach. The formulated ODTs were found to have a pleasant taste as confirmed by the taste panel[11]. Singh *et al.*, masked the bitter taste of etoricoxib by complexation with weak cation exchange resins (Indion 214, 234 and 414) in order to increase its compatibility and patient compliance. Indion 234 resin was found to possess good taste masking ability compared to Indion 214 and 414 during a sensory taste evaluation test.[44]

Puttewar *et al.*, successfully utilized Indion 234 to prepare taste masked orally disintegrating tablets of doxylamine succinate. Batch method was employed to prepare drug–resin complex and complexation was optimized for various processing parameters viz. drug–resin ratio, pH, temperature and drug concentration to achieve maximum drug loading. Drug–resin ratio of 1:2, pH 5, temperature 50 °C and 4 mg/ml drug concentration were found to be optimum for obtaining maximum loading. Drug release in 0.01 N hydrochloric acid and in simulated salivary fluid indicated successful taste masking of resinate. The optimized batch F5 was found to have disintegration time of 25.24 ± 0.75 sec and dissolution 100.46% ± 3.78 and was found to have better taste in comparison to conventional marketed formulation.[45] Prajapati *et al.*, masked the bitter taste of sumatriptan succinate by ion exchange with Kyron T 114 as ion exchange resin. The resinates were formulated into sublingual tablet formulation by direct compression and evaluated for various parameters. The optimized batch

disintegrated in vitro within 28-34 sec and the maximum release was obtained in 14-15 min. The optimized tablet formulation showed better taste and the formulated sublingual tablets may act as a potential alternate for the sumatriptan succinate oral tablet.[46] Yewale *et al*., masked the bitter taste of Chlorpheniramine maleate using cation exchange resins prepared by batch process. Drug: resin ratios 1:1, 1:2, 1:3 and 1:4 (w/w) were used to prepare the complexes of ion-exchange resin and Chlorpheniramine maleate. The optimum drug:resin ratio and the time required for maximum complexation was determined. The drug resinates were characterized by FTIR, DSC and X-ray diffraction (PXRD) and also evaluated for the drug content, taste and drug release. The taste evaluation depicted the successful taste masking of Chlorpheniramine maleate with DRCs. The optimized drug resin with a ratio 1:2 was formulated into fast disintegrating tablets (FDTs) and was found to have a drug release of 94.77% in 30 min.[47]

Jumde *et al.,* developed verapamil hydrochloride resinates by ion exchange resin complexation and further investigated the effect of electric current (0.1-10 mA) on the complexation of drug. In comparison to conventional methods, the direct current (DC) (1 mA) applied during activation or complexation alone or both demonstrated significant increase in verapamil hydrochloride-resin complexation. Further increase in intensity of current above 1 mA failed to enhance the drug binding. Thus use of electric current can be used as a novel batch method for the preparation of drug-resinates.[48] Aman *et al.,* developed a stable controlled release resinate-complex for the highly bitter taste famotidine to allow once-daily administration and improve patient compliance especially in pediatric and geriatric medicine. The drug-resinate complexes in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 were prepared using Amberlite IRP-69 as an ion exchange resin. Maximum drug loading and sustained release property was shown by drug resin complex in the ratio of 1:6 which was further subjected to physicochemical characterizations by DSC, XRD, FTIR and SEM. The optimized complex was uniformly dispersed in the prepared syrup and the resulting suspension was subjected to accelerated stability study. The formulated suspension was found to have better taste masking properties as revealed by human taste panel studies.[49]

It is evident from the various reported work as explained above that the technique of ion exchange resin complexation is a very useful and most commonly used technique for masking the bitter taste of various drugs such as ranitidine, ciprofloaxacin, roxithromycin, risperdone, ondansetron and donzepezil hydrochloride.

Table 1: Commonly used ion exchange resin for taste masking

Type	Functional group	Polymer backbone	Commercial resins
Strong anion	$-N^{+}R3$	Polystyrene-DVB	Amberlite IR 400, Dowex 1
Weak anion	$-N^{+}R2$	Polystyrene-DVB	Amberlite IR 4B, Dowex 2
Strong cation	-SO3H	Polystyrene-DVB	Amberlite IR 120, Dowex 50, Tulsion 344
Weak cation	-COOH	Methacrylic acid-DVB	Amberlite IR 64, Indion 204, 234, Tulsion 335, 339

Table 2: Application of ion-exchange complexation in taste masking.

Drug	Resin used	Dosage form	Reference
Chlorpheniramine maleate	Indion CRP 244,254	Resinates in powder form	23
Ranitidine HCl	Amberlite IRP 69/88	Chewable tablet	24
Buflomedil	Amberlite IRP 69	Resinates in powder form	25
Orbifloxacin	Amberlite IRP64/69	Dry/liquid suspension	26
Risperidone	IRP-64	Fast disintegrating tablet	27
Quinine sulphate	Amberlite IRP	Oral suspension	28
Roxithromycin	Indion 214 and 204	Mouth-dissolve tablet	29
Dextromethorphan	Amberlite IRP 69	Fast melting tablet	30
Risperidone	Amberlite IRP-64	Resinates in powder form	31
Ondansetron hydrochloride	Indion 234	ODT	32
Etoricoxib	Indion 204	Resinates in powder form	33
Donzepezil hydrochloride	Amberlite IRP 64	ODT	34

CONCLUSION

Ion exchange resins have shown tremendous potential in pharmaceutical product development and are currently finding a lot of applications in pharmaceutical formulations. In the present article, the authors have reviewed the application of ion exchange resin complexation in the taste masking of bitter drugs. The literature revealed that the technique of ion exchange resin is a very simple and practical approach to mask the bitter taste of several bitter taste medicaments thereby improving their compliance by patients. The major highlight of this technique is that the taste is masked without interfering with the release of drug in gastric environment which make it very suitable technique for taste masking of immediate release dosage forms meant for oral administration. Thus ion exchange resin will continue to show its worth as one of the most significant taste masking approach.

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