Ion Exchange Resins: An Novel Approach towards Taste Masking of Bitter Drugs and Sustained Release Formulations with Their Patents

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ABSTRACT

The main purpose of this review article is to cover various aspects related with the use of ion exchange resins for taste masking of bitter drugs and also for formulation of sustained release dosage form. Ion exchange resins are water insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain and have the ability to exchange counter-ions within aqueous solutions surrounding them. The bitterness of pharmaceutical medicines plays a critical role in patient compliance, as the oral administration of bitter drugs is often hampered by their unpleasant taste which leads to non-compliance. One of the popular approaches in the taste masking of bitter drugs is based on IER. For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug. The drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. Sustained release dosage forms are designed to release a drug at a pre determined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. Research over the last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical and taste masking. The major drawback of sustained released formulation is dose dumping, resulting in increased risk of toxicity. The use of IER has occupied an important place in the development of controlled- or sustained-release systems because of their better drug-retaining properties and prevention of dose dumping. Synthetic ion exchange resins have been used in pharmacy and medicine for taste masking or controlled release of drug. Drug resin complexation converts drug to amorphous form leading to improved drug dissolution. The review also incorporates various patents related to taste masking and sustained release formulations using IER.

KEYWORDS

Ion exchange resins, Taste masking, sustained release, Bitterness, patents
1. INTRODUCTION
Ion exchange resins are water insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain and have the ability to exchange counter-ions within aqueous solutions surrounding them [1]. One of the popular approaches in the taste masking of bitter drugs is based on Ion Exchange resin (IER). IER are solid and suitably insoluble high molecular weight poly-electrolytes.

**Figure 1:** Ion Exchange Resins

These are small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate backbone.

- The material has a highly developed structure of pores on the surfaces from where the ions are trapped or released. The trapping of ions takes place only with simultaneous release of other ions; thus, the process is called ion exchange.
- Ion exchange resins have found applications in overcoming various formulation-related problems including poor stability and poor dissolution, for taste masking and as a powder processing aid. Moreover, ion exchange resins can also be used for modifying the drug release from the formulation [1].

1.2 Chemistry of Ion Exchange Resins
An ion exchange resin is a polymer (normally styrene) that contain solids with charged sites that exchange ions, and certain minerals called zeolites are quite good exchangers. While there are numerous functional groups that have charge, only a few are commonly used for man-made ion exchange resins. These are:

1. -COOH, which is weakly ionized to \(-\text{COO}^-\)
2. -SO\(_3\)H, which is strongly ionized to \(-\text{SO}_3^-\)
3. -NH\(_2\), which weakly attracts protons to form \(\text{NH}_3^+\)
4. -secondary and tertiary amines that also attract protons weakly
5. -NR\(_3^+\), which has a strong, permanent charge (R stands for some organic group)

1.3 Mechanism of Ion Exchange Process (Physical Chemistry View)
The ion-exchange reaction is a reversible, selective and stoichiometric interchange of mobile ions of like charges between the ion-exchanger and the external liquid phases. Each counter-ion that is released from the ion-exchanger is replaced by an equivalent amount of another ionic species of same sign and valence due to the electro neutrality requirement. Based on the nature of the ionic species being exchanged.

\[
\text{Ion-exchanger } A^+ + B^- \rightleftharpoons \text{Ion-exchanger}^+ B^- + A^-
\]

When the ion-exchanger is placed in an electrolyte solution containing counter-ions which are different from those bound to the ion-exchanger, the migration of the first few external ions into the ion-exchanger and bound ions into the surrounding external solution creates an electrical potential difference (Donnan potential) between the ion exchange and the external solution phases. The created Donnan potential accomplishes the interchange of counter-ions between the two phases until an equilibrium stage (Donnan equilibrium) is reached, that is, the equality of electrochemical potentials for each mobile ion between the phases. The higher the Donnan potential, the stronger is the co-ion exclusion from the ion-exchanger and, on the other hand, the stronger is the attraction of counter-ions towards the ion-exchanger. In a concentrated external solution the Donnan potential is low and, thus, the interaction between the mobile counter-ion and the ion exchange is weak, achieving high rates of ion-exchange. In addition to the concentration of the surrounding solution, the Donnan potential is dependent on the selectivity and capacity of the ion-exchanger, the charge of the ions present, and the pressure.

1.4 Kinetics of Ion Exchange Process

The ion-exchange is essentially a diffusion process, but is also related to chemical reaction kinetics. It can be described as a series of consecutive reaction and mass transfer processes. The steps are as follows:

- Film diffusion - the exchangeable counter-ion must diffuse through the adherent external solution to the surface of the ion-exchanger.
- Particle diffusion - Then it should diffuse within the ion-exchange material, to the ionized
The actual ion-exchange reaction between the mobile counter-ions occurs at the fixed ionic binding site.

Finally, the released counter-ion diffuses from the ionic binding site into the surrounding solution by particle and film diffusion.

The rate of the ion-exchange process is determined by the slowest of these five steps. In most of the cases, the rate- determining step (RDS) of the ion-exchange is the diffusion of the larger ion (e.g. drug-ion) within the polymer framework [5].

1.5 Physiology of Taste

![Anatomy of Taste Buds](image)

**Figure 3:** Anatomy of Taste Buds [6]

1.5.1 Taste – Ability to Respond to Dissolved Molecules and Ions in Mouth.

Biologically taste is also known as gestation. It is a chemical reaction arising from sensory responses of four main taste perceptions: sweet, bitter, salt, sour [7].

1.5.2 Taste Buds

Taste buds and taste papillae: Taste papillae can be seen on the tongue as little red dots, or raised bumps, particularly at the front of the tongue. These ones are actually called "fungiform" papillae, because they look like little button mushrooms. There are three other kinds of papillae, foliate, circumvallate and the non-gustatory filiform. You can see that the taste buds are collections of cells situated on top of, or on the sides of, the different papillae. Taste buds are situated on the taste papillae (middle section). At the base of the taste bud, afferent taste nerve axons invade the bud and ramify extensively, each fibre typically synapsing with multiple receptor cells within the taste bud [8].

**Location of Taste Buds**

- Salty taste- located on the edge and upper front portions of the tongue.
- Sweet taste- they are found on the tip of the tongue.
- Sour taste - they occur at the sides of tongue and are stimulated by acids.
- Bitter taste- located towards the back of tongue [9].
1.5.3 Taste Nerves
Taste nerves or gustatory nerves are a network of dendrites of sensory nerves which are interwoven among the taste cells.

1.5.4 Signalling to Brain
When taste cells are stimulated by binding of chemicals to their receptors, they depolarise and this depolarisation is transmitted to the brain. Once taste signals are transmitted to brain, several efferent neural pathways are activated that are important for digestive functioning.

1.5.5 Taste Receptors for Bitter Taste
The bitter taste results from binding of diverse molecules to a family of about 30 T2R receptors [6].

1.5.6 Bitterness of Drugs and Patient Compliance Dysgeusia
The medical term for changes in taste is dysgeusia. Medications often bring on dysgeusia by altering the way the body detects food, giving it bitter, salty or metallic taste. This annoying side effect is common among older patients as they frequently take several medications. Once the medication is discontinued, these taste sensations usually will disappear. There are several reasons a person may notice a metallic taste in their mouth. Sometimes a tooth infection or bacteria in the mouth's mucus membrane are the cause. Several medications also can bring on this strange side effect.

The bitterness of pharmaceutical medicines plays a critical role in patient compliance, as the oral administration of bitter drugs is often hampered by their unpleasant taste which leads to non-compliance and further worsening of diseased condition. Unwillingness to swallow solid dosage form such as tablets is a general problem for all age groups, especially elderly and pediatrics mainly due to the physiological changes. Among various approaches two are commonly used to diminish the bitter taste of drug:

- By reducing the solubility of drug in the pH of saliva (5.6-6.8).
- By altering the affinity and nature of drug which will interact with the taste receptor [11].

1.6 Taste Masking and Its Advantages
Taste Masking – apparent reduction in the unpleasant taste by using a suitable agent

Taste masking technology includes two aspects –

- Selection of suitable taste masking substance such as polymers, sweeteners, flavors, amino acids etc.
- Selection of suitable taste masking techniques.

A suitable taste masking technique can powerfully impact both, quality of taste masking and process effectiveness. There are many techniques developed for taste masking of bitter drugs. They are as follows:

- Addition of flavoring and sweetening agents.
• Complexation with ion-exchange
• Micro encapsulation.
• Prodrug approach
• Inclusion complexation
• Granulation [6].

1.7 Advantages of Taste Masking

Some of the advantages of taste masked tablets include:-

• Taste masking of bitter drugs improve patient’s compliance.
• It also improves the stability of some drugs
• It also improves the therapeutic efficacy.
• It also improves the bioavailability of certain drugs.
• It also improves the organoleptic characteristics of drugs [13].

1.8 Ion Exchange Resins as an Approach towards Taste Masking

• 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 poly electrolytes that can exchange their mobile ions of equal charge with the surrounding medium.
• 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 40 meq / 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.
• The drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected [14].

1.9 Advantages of Resins as Taste Masking Agents

1. Resins being poly electrolytes have extensive binding sites leading to very high drug loading ability.
2. They are chemically inert and free from local and systemic side effects.
3. All conventional solid, semisolid and liquid dosage forms can be prepared by using resins.
4. They have been used in selective separation of pharmaceuticals from mixtures.
5. Being stable to all sterilization means, can be formulated into all sterile dosage forms [15].

1.10 Evaluation Techniques Taste Masked Drug-Resin Complex

To quantitatively evaluate taste sensation, following methods have been reported in literature-

1) Panel Testing

The panel testing is a psychophysical rating of the gustatory stimuli. In this method, a group of about 5 to 10 human volunteers is trained for taste evaluation by using reference solutions ranging in taste from tasteless to very bitter. Numerical values are then assigned to these levels of bitterness. Subsequently, test solution is tasted and rated on the same scale to assess its bitterness.
2) **Measurement of Frog Taste Nerve Responses**
In this method, adult bull frogs are anaesthetized intraperitoneally and the gloss pharyngeal nerve is then located and dissected from the surrounding tissue and cut. An AC amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

3) **Multichannel Taste Sensor / Magic tongue**
This is an automated taste sensing device to detect the magnitude of bitterness of a drug substance. The device has a transducer which is composed of several kinds of lipid/polymer membranes with different characteristics that can detect taste in a manner similar to human gustatory sensation. Taste response is transferred into a pattern composed of electric signals of membrane potentials of the receptor part. Different response electric potential pattern are obtained for substance producing different taste qualities.

4) **Spectrophotometric Method**
A known quantity of the taste masked formulation is mixed with 10 ml of distilled water in 10 ml syringe by revolving the syringe, end to end; five times in 30 seconds. The test medium is then filtered through a membrane filter, followed by spectrophotometric determination of the concentration of the drug in the filtrate. If this concentration is below the threshold concentration, it may be concluded that the bitter taste would be masked in vivo. This technique has been applied to evaluate the taste masked granules of sparfloxacin, with threshold concentration being 100 μg / ml [16].

1.11 **Approach towards Sustained Release Formulations Using Ion Exchange Resins**
An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic levels of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment [38]. The frequency of administration or the dosing interval of a drug depends upon its half-life and therapeutic index. With many drugs the basic goal is to achieve a steady – state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage regimens is an important element in accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a control over uncertain fluctuations in the in vivo environment where the drug is released. This can be achieved by approaches to drug delivery systems. One such approach is sustained release drug delivery system.

1.11.1 **Sustained Release Formulations**
Sustained release dosage forms are designed to release a drug at a predetermined rate and prolonged therapeutic effect over an extended period of time in order to maintain a constant drug concentration for a specific period of time with minimum side effects [39].
1.11.2 Advantages of Sustained Release Formulations

- Improved patient compliance – since the frequency of drug administration is reduced.
- A more even blood level is maintained – as the blood level oscillations characteristics of multiple dosing of conventional dosage form is reduced.
- Maximizing availability with a minimum dose – the total amount of drug administered is reduced.
- Better control on drug absorption – in case of drug with high bioavailability, the high blood level peaks observed after administration can be reduced by formulating into an extended action form.
- Increased safety margin of high potency drugs – safety margin of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Increased reliability of therapy [40]
**Figure 5:** Classification of Ion Exchange Resin

**Table 1:** Drugs with Metallic Taste [12]

<table>
<thead>
<tr>
<th>Category of Drugs</th>
<th>Allergy (antihistamine) medicines</th>
<th>Antibiotics</th>
<th>Antifungals</th>
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<th>Blood pressure medications</th>
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<tbody>
<tr>
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<td>Chlorpheniramine maleate</td>
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</tr>
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<td></td>
<td></td>
<td>leomycin</td>
<td>Griseofulvin</td>
<td></td>
<td>Diltiazem, a calcium channel blocker,</td>
</tr>
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<td></td>
<td></td>
<td>Cefamandole</td>
<td>Metronidazole</td>
<td></td>
<td>Enalapril, Cholesterol-lowering drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levofloxacin (Levaquin)</td>
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<td>Clofibrate</td>
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<td></td>
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<td></td>
<td>PD</td>
</tr>
</tbody>
</table>
### Examples of Drugs

- DMSO
- Glipizide
- Allopurinol
- Iron (given by injection)
- Sorbitex
- Levodopa

### Table 2: Examples of Taste Masked Drugs Using IER [11]

<table>
<thead>
<tr>
<th>Commercial resin</th>
<th>Matrix</th>
<th>Functionality</th>
<th>Ionic form</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amberlite IR 120, Dowex 50, Indion 244, Purolite C100 HMR, Kyron-T-154</td>
<td>Styrene DVB Polymer</td>
<td>SO3H</td>
<td>Strong cation</td>
<td>Erythromycin Stearate</td>
</tr>
<tr>
<td>Amberlite IRP 69,</td>
<td>Sodium Styrene DVB Polymer</td>
<td>SO3Na</td>
<td>Strong cation</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Amberlite IRC 50, Indion 204, Purolite C102D, Kyron-T-104, Tulsion T-335, Doschion P 544 (R)</td>
<td>Methacrylic acid DVB Polymer</td>
<td>-COOH</td>
<td>Weak cation</td>
<td>Spiramycin, Ranitidine, Dextromethorphan, Dimenhydrinate, Roxithromycin,</td>
</tr>
<tr>
<td>Amberlite IRP 88, Indion 234, Tulsion T-335</td>
<td>Methacrylic acid DVB Polymer</td>
<td>-COOK</td>
<td>Weak cation</td>
<td>Ciprofloxacin, Chloroquine phosphate, Metronidazole, Azithromycin, Quinine Sulphate</td>
</tr>
<tr>
<td>Patent no.</td>
<td>Title</td>
<td>Drug</td>
<td>Inventor, year</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>WO2012/120522A1</td>
<td>A taste masked chewable tablet of sildenafil</td>
<td>Sildenafil</td>
<td>Murpani D., 2012 [18]</td>
<td></td>
</tr>
<tr>
<td>Patent/Document</td>
<td>Description</td>
<td>Active Drug</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
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<td>-------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>US 2006/0204559</td>
<td>Fast dissolving orally consumable films containing an ion exchange resin as a taste masking agent</td>
<td>Dextromethorphan</td>
<td>Bess W. S., et al 2001</td>
<td></td>
</tr>
<tr>
<td>US 20050036977</td>
<td>Taste masked resin ate and preparation there of</td>
<td>Active drug</td>
<td>Gole D., et al 2005</td>
<td></td>
</tr>
<tr>
<td>US 5032393</td>
<td>Drug adsorbates</td>
<td>Ranitidine</td>
<td>Douglas S.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4: Patented work on Resonates for Sustained Released Formulation

<table>
<thead>
<tr>
<th>Patent no.</th>
<th>Title</th>
<th>Drug / polymer</th>
<th>Inventor, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent Number</td>
<td>Description</td>
<td>Drug Formulations</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>USP 20060263431</td>
<td>Opioid Sustained Release Formulation</td>
<td>Oxycodone, meperidine, methadone, nalbuphine, opium, pentazocine, propoxyphene/ styrene-divinylbenzene</td>
<td>Maloney A. M., 2006 [51]</td>
</tr>
<tr>
<td>USP 20050265955</td>
<td>Sustained release preparations</td>
<td>hydrocodone bitartrate / Dowex 50WX8H</td>
<td>Raman S. N., et al, 2005 [52]</td>
</tr>
<tr>
<td>USP20020164373</td>
<td>Opioid Sustained Release Formulation</td>
<td>butorphanol, fentanyl, codeine, dihydrocodeine, hydrocodone bitartrate/ hydroxyalky cellulose / styrene-divinylbenzene</td>
<td>Maloney A. M., 2002 [54]</td>
</tr>
<tr>
<td>USP 6258350</td>
<td>Sustained release ophthalmic formulation</td>
<td>pilocarpine, epinephrine, etc. /poly (styrenedivinyl) benzene</td>
<td>Mallick S., 2001 [55]</td>
</tr>
<tr>
<td>EP0429732</td>
<td>Sustained</td>
<td>Betaxolol, timolol, befunolol, etc. / Amberlite, Dowex</td>
<td>Jani R., Harris R. G., 1991 [57]</td>
</tr>
</tbody>
</table>
1.11.3 Disadvantages of Sustained Released Formulation

- Do not permit prompt termination of therapy – immediate change in drug need required during therapy (such as might be encountered if significant adverse effects are noted) cannot be accommodated.
- Less flexibility in adjusting dosage regimens.
- No consideration of diseased patients – these are designed for normal population on the basis of average biologic halve – lives, so diseased patients and significant patient’s variation are not accommodated.
- Economic factors – more costly processes and equipments are involved.

1.12 Role of Ion Exchange Resins in Sustained Drug Delivery Systems

The usage of IER during the development of sustained release formulations plays a significant role because of their drug retarding properties and prevention of dose dumping. The drug resonates can also be used as drug reservoirs, which causes a change in drug release characteristics. The slowness of uptake and release of medicament from ion exchange resin has proved to be effective in solving the problem of dose dumping by conventional dosage form. Ion exchange resins are extremely insoluble in aqueous liquids and have no side effects unless given in large dosage enough to disturb the calcium and sodium balance of body fluids as they have an affinity for these ions [41].

1.13 Some Properties Which Make Ion Exchange Resin a Suitable Candidate for SRDDS

- Physico-chemical stability
- Inert nature
- Uniform size
- Spherical shape assisting coating
- Equilibrium driven reproducible drug release in ionic environment.

1.14 Mechanism of Release

Drug from loaded resonates occurs through exchange of appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resonate into the gastrointestinal environment. Similar principle can be applied for release at other administrations sites. The equation for drug – ion exchange can be represented as follows-

\[
\text{Resin - Drug}^+ + X^+ \Leftrightarrow \text{Resin -X}^+ + \text{Drug}^+ \\
\text{Resin - Drug}^- + Y^- \Leftrightarrow \text{Resin - Y}^- + \text{Drug}^- \\
\]

Where, X and Y are ions in the gastrointestinal tract.

- The prolonged release of the active drug is accomplished by providing a semi permeable coating around discrete, minute, ion exchange resin particles with which the drug component has been complexed to form an insoluble drug resin complex.
The semi-permeable coating creates a diffusion barrier and the thickness of which can be adjusted to provide the desired level of retardation of drug availability in the gastrointestinal tract over a period of time.

Several preparations involving strong resonates of sulphuric acid (cation exchange resins) provided more moderate release than the weak resonates of carboxylic acid. Hence, resonates of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.

1.15 Evaluation of Drug Resonates

Evaluation of drug resonates involves in vitro and in vivo testing of the drug loaded resonates.

1) In vitro Evaluation

The in vitro test demonstrates the release pattern of a drug from resinate preparation dosage form. Tests developed for this purpose are limited to dissolution testing using dissolution test apparatus as per the dosage form. Drug release depends on size of resinate, degree of cross linkage of resin with drug, nature of the resins, nature of the drug and test conditions that is ionic strength of the dissolution medium.

Significance of in vitro Evaluation

- Data from such tests are required as a guide to formulation during the development stage prior to clinical testing.
- It is necessary to ensure batch – to – batch uniformity in the production of a proven dosage form.

2) In vivo Evaluation

In vivo procedures used for estimating drug activity of resonates include serum concentration level determination, urinary excretion, and toxicity studies [42].

1.16 Regulation of Ion Exchange Resins for the Food, Water and Beverage Industries

The FDA has the responsibility to define conditions under which safe food additives may be used in the production and preparation of foods and beverages. These conditions are written in the CFR, title 21, part 173 (secondary direct food additives permitted in food for human consumption). Section 25 of this part deals specifically with the use of ion exchange resins. The three major conditions spelled out by this law are:

(1) The resins must be one of a preapproved generic list of resin compositions (listed in 21 CFR 173.25), of which the ingredients used to produce the resins comply with FDA food additive regulations;

(2) The resin must be 'subjected to preuse treatment by the manufacturer and/or user in accordance with the manufacturer's directions';

(3) The resin must be 'found to result in no more than 1 part per million of organic extractives [57].
2. CONCLUSION

Ion exchange resins are the most useful for taste masking of bitter drugs and for sustained release preparations. By using the IER one can easily prepare a dosage form like suspensions, tablets etc. In future there is much scope for the preparations with exchange resins in pharmaceuticals.

Taste masking of drug by ion exchange resin is economical, simple and convenient method. Various techniques are used to mask the bitter taste of drug. But one of the most Economical method 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 sigmoid Release, floating, pH and ionic strength-responsive systems, have shown the potential use of IER in drug delivery.

3. REFERENCES


50. Maloney A.M. Opioid Sustained Release Formulation. USP 20060263431; 2006.