ION EXCHANGE RESINS: AN APPROACH TOWARDS TASTE MASKING OF BITTER DRUGS AND SUSTAINED RELEASE FORMULATIONS WITH THEIR PATENTS

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ABSTRACT

The purpose of this review is to cover various aspects related with the use of ion exchange resins for taste masking of bitter drugs and for formulating 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 and further worsening of diseased condition. 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. The usage of IER during the development of sustained release formulations plays a significant role because of their drug retarding properties. In this 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

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 them¹.

Figure 1: Ion Exchange Resins²

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 formulation¹.

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:

-COOH, which is weakly ionized to -COO^-

-SO₃H, which is strongly ionized to -SO_3^-

-NH₂, which weakly attracts protons to form NH_3^+

-secondary and tertiary amines that also attract protons weakly

-NR₃⁺, which has a strong, permanent charge (R stands for some organic group). These groups are sufficient to allow selection of a resin with either weak or strong positive or negative charge³.

Mechanism of Ion Exchange Process (Physical Chemistry View)

Figure 2: Ion Exchange Process⁴

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, the ion-exchange process is either anionic or cationic.

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.

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 functional groups.

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 framework⁵.

Physiology of Taste

Figure 3: Anatomy of Taste Buds⁶

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

Biologically taste is also known as gustation. It is a chemical reaction arising from sensory responses of four main taste perceptions: sweet, bitter, salt, sour⁷.

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 nongustatory 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 bud⁸.

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 tongue⁹.

Taste Nerves

Taste nerves or gustatory nerves are a network of dendrites of sensory nerves which are interwoven among the taste cells.

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.

Taste Receptors for Bitter Taste

The bitter taste results from binding of diverse molecules to a family of about 30 T2R receptors⁶.

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.

Antibiotics

Antibiotics are frequently the cause of a metallic taste. The following antibiotics sometimes cause a metallic taste: Ampicillin, a member of the penicillin group and a treatment for common bacteria causing infections such as bladder infections and ear infections; tetracycline treats infections and acts to control acne; and bleomycin, an injectable medication is used in chemotherapy treatment. Cefamandole kills bacteria and prevents their growth, while levofloxacin treats

infections and is used following anthrax exposure. Lincomycin is used for serious infections and works by preventing production of proteins needed by certain bacteria.

Blood Pressure Medications

As a major segment of the population ages, prescription of blood pressure and blood thinner medications is becoming more common. ACE inhibitors such as captopril and enalapril are in this group of drugs. ACE means angiotensin-converting enzyme. Captopril and enalapril are both used to treat congestive heart failure, high blood pressure and to improve the odds of surviving a heart attack. Diltiazem is a channel blocker medication used to slow the heart's rhythm and to treat angina and high blood pressure. These are all known to produce a metallic taste side effect.

Thyroid and Diuretics

Some thyroid drugs also produce a metallic taste. Carbimazole is a drug used to treat hypothyroidism and thyroid inflammation. Methimazole is also prescribed for an overactive thyroid gland or in preparation for thyroid surgery. Amiloride is a diuretic that is often prescribed to restore potassium levels by restricting how much sodium the body absorbs. Amiloride also causes food to have a metallic taste.

Muscle Relaxers

Several muscle relaxers can affect the taste of food or produce a residual metallic taste. Baclofen is prescribed for muscle spasms often caused by multiple sclerosis. Another muscle relaxant with the same side effect is chlormezanone, a sedative and muscle relaxant¹⁰. Palatability of the active pharmaceutical ingredient is a very important technical obstacle to develop a patient friendly formulation. 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 receptor¹¹

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

- Multiple emulsion technique
- Gel formation
- Bitterness inhibitors
- Miscellaneous⁶

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 drugs¹³.

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 affected¹⁴.

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 sterilisation means, can be formulated into all sterile dosage forms¹⁵.

Evaluation Techniques Taste Masked Drug- Resin Complex

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

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.

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

proximally. 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.

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.

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 / ml¹⁶.

Patents Related to Tasty Masking of Drugs with IER WO 2012/167878 A1

An edible oral film strip dosage form containing an unpalatable acidic active pharmaceutical ingredient, particularly ketoprofen, and an ion exchange resin as a primary taste masking agent, along with an optional alkaline agent and further optionally containing one or more secondary taste masking agents is provided. The edible oral film strip dosage matrix is formed from at least one water soluble or miscible polymer (s). The optional secondary taste masking ingredients include one or more of flavouring agent(s), sweetener(s), cooling sensation agent (s), and taste receptor blocker (s). The inventive dosages minimize or completely mask the bitterness, burning sensation and throat irritation associated with many acidic active pharmaceutical ingredients. Methods for preparing the inventive edible oral film strip dosage forms are disclosed, as well as their method of administration¹⁷.

WO2012/120522A1

A taste masked chewable tablet of sildenafil and the process of its preparation¹⁸.

WO2011/080683A1

The present invention relates to taste masked dosage forms of bitter tasting anti- retroviral drugs comprising a complex of the said anti-retroviral drug and an ion-exchange resin and one or more of other pharmaceutically acceptable excipients. It further relates to the processes for the preparation thereof¹⁹.

WO2011/030351A2

The present invention relates to taste-masked pharmaceutical compositions comprising phosphodiesterase-5 (PDE-5) inhibitors. The taste-masked pharmaceutical compositions for oral administration comprise at least one PDE-5 inhibitor, at least one taste-masking agent; and at least one pharmaceutically acceptable excipient. Further the taste-

masked PDE-5 inhibitor compositions are provided in the form of palatable formulations suitable for oral administration such as orally disintegrating tablets, bite-dispersion tablets, chewable tablets, dispersible tablets, effervescent tablets or the like. The invention also further relates to method for masking the objectionable taste of PDE-5 inhibitor²⁰.

US2011/0300224A1

A taste masked dosage form of pharmaceutical acceptable salt of escitalopram comprising (a) resin complex of pharmaceutical acceptable salt of escitalopram and cationic exchange resin or adsorbing or coating non-pareil seeds or inert particles with a mixture of pharmaceutically acceptable salt of escitalopram, cationic polymer and optionally other polymer (s) or loading non-pareil seeds or inert particles with pharmaceutically salt of escitalopram followed by polymer coating with cationic polymer and optionally other polymer(s); and (b) at least one pharmaceutical excipient²¹.

US80088378B2 and US2008/0044371A1 and WO2005/013934A2

The present invention provides a taste-masked composition containing an active compound. The composition is taste-masked by employing a loaded polymeric matrix which is produced by incorporating or complexing the active compound on a polymeric matrix having ionic functional groups and removing unbound active compounds from the polymeric matrix^{22,23,31}.

WO2010/150221A1

The invention provides taste masked pharmaceutical compositions comprising pregabalin or salts or enantiomers thereof. The invention also relates to the process of preparation of such compositions²³.

WO2009/074995A1

The present invention relates to chewable solid pharmaceutical compositions comprising sildenafil citrate. Sildenafil citrate is a very bitter drug, hence the conventional tablets, comprise of a film coating for aesthetic appearance and acceptability. Chewable tablets are usually uncoated and hence there is a need to mask the bitter taste of sildenafil to ensure patient acceptability. The present invention achieves the taste masking of sildenafil citrate by using an ion-exchange resin which forms a complex and masks the bitter taste of sildenafil. The ion-exchange masked sildenafil complex is then incorporated with other excipients to formulate a chewable tablet using flavours and other ingredients²⁴.

US 2008/0095842 A1

A resinate of Cetirizine or its pharmaceutically acceptable salts or its enantiomers or their salts such as Levocetirizine Dihydrochloride, fast disintegrating and or quick release pharmaceutical compositions containing the resinate and the process for the preparation of the said resinate and composition is disclosed. Preparation of resinate and composition comprising resinate is carried out preferably in aqueous²⁶.

WO2007/146293A3

The present invention relates to a taste-masked composition of an active pharmaceutical ingredient (API) for oral delivery and a related method for the preparation of the taste-masked

composition comprising a granulated mixture of the active pharmaceutical ingredient, an insoluble matrix component, a film-forming agent, and a water soluble binder²⁷.

US 2006/0204559 and WO01/70194A1

It involves physiologically acceptable films, including edible films. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as Amberlite. Methods for producing the films are also disclosed^{28,34}.

US 20060115529

It involves fast melting tablets contain particles of an active ingredient and ion – exchange resin complex to mask unpleasant taste associated with the active ingredient. The resin complex particles can be coated or uncoated to impart sustained release properties to the active ingredient. A fast melting tablet also comprises a dry binder and bulk diluent to form highly plastic granules that are subsequently compressed into tablets²⁹.

US 20050036977

It is directed to a taste masked resinate that contains a water insoluble active substance complexed to an ion – exchange resin in a taste masking effective amount. The taste masked resinate is useful in the manufacture of a dosage form such as rapid – disintegrating tablet, a rapid disintegrating film, an effervescent tablet, a chewable tablet, a chewing gum, a suspension, a sprinkle granule, a powder for reconstitution in a suspension and the like and a method for the preparation thereof³⁰.

US 6,565,877, B1

It involves a taste masked composition which comprises a bitter tasting drug, a combination of two enteric polymers comprising, a methacrylic acid polymer and a phthalate polymer is described. The composition of present invention is prepared by dissolving the active ingredient, the methacrylic acid copolymer and the phthalate polymer in a solvent and recovering the composition from the solution thereof³².

US 6,514,492 B1

It relates to the formulation of oral liquid products of quinolones or derivatives thereof using ion exchange resins, such as methacrylic acid polymer Cross linked with divinylbenzene, as the carrier, thereby eliminating the extreme bitterness of the quinolones oral liquid formulation³³.

US 5032393

It describes the bitter taste of ranitidine may be masked by forming an adsorbate with a synthetic cation exchange resin. The adsorbate is particularly suitable for use in pharmaceutical compositions for oral administration such as chewable or suckable tablets, granules and aqueous or non – aqueous suspensions³⁵.

EP0212641

This invention relates to drug-polymer matrix compositions comprising an active ingredient having an amino or amido group and a pharmaceutically acceptable copolymer having a plurality of carboxylic acid and ester groups wherein the

matrix dissociates in a media having a pH of less than 4, thereby releasing the active ingredient into the media³⁶.

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 treatment³⁸. 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.

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 effects³⁹.

Figure 8: Comparative Blood Drug Level Profiles of Different Delivery Systems

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 a 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 therapy⁴⁰

Table 1: Drugs with Metallic Taste¹²

Category of Drugs	Allergy (antihistamine) medicines	Antibiotics	Antifungals	Asthma medicines	Antipsychotics	Blood pressure medications
Examples of Drugs	Chlorpheniramine maleate	Ampicillin leomycin Cefamandole Levofloxacin (Levaquin) Lincomycin Tetracycline	Amphotericin B Griseofulvin Metronidazole	Bamifylline	Lithium Trifluoperazine	Captopril, an ACE inhibitor Diltiazem, a calcium channel blocker, Enalapril, an ACE inhibitor
Category Of Drugs	Blood thinners	Diuretics	Glaucoma medication	Heart medication	Bisphosphonates	Cholesterol-lowering drugs
Examples of Drugs	Dipyridamole	Amiloride Ethacrynic acid	Acetazolamide	Nitroglycerin patch	Etidronate	Clofibrate
Category Of Drugs	Corticosteroids (used to treat inflammation)	Diabetes medications	Gout medications	Iron-deficiency anemia medication	Muscle relaxers	Parkinson's disease medications
Examples of Drugs	Dexamethasone (DMSO) Hydrocortisone	Glipizide	Allopurinol Colchicine	Iron Sorbitex (given by injection)	Baclofen Chlormezanone	Levodopa
Category of Drugs	Seizure medications	Thyroid medicineS	Transplant rejection drugs	Tuberculosis medications	Smoking cessation products	Stimulants
Examples of Drugs	Carbamazepine Phenytoin	Carbimazole Methimazole	Azathioprine	Ethambutol	Nicotine skin patch	Amphetamine

Table 2: Examples of Taste Masked Drugs Using IER¹¹

Commercial resin	Matrix	Functionality	Ionic form	Examples of Drugs
Amberlite IR 120, Dowex 50, Indion 244, Purolite C100HMR, Kyron- T- 154	Styrene DVB Polymer	SO ₃ H	Strong cation	Erythromycin Stearate
Amberlite IRP 69,	Sodium Styren DVB Polymer	SO ₃ Na	Strong cation	Ranitidine
Amberlite IRC 50, Indion 204, Purolite C102D, Kyron-T- 104, Tulsion T- 335, Doshion P 544 (R)	Methacrylic acid DVB Polymer	-COOH	Weak cation	Spiramycin, Ranitidine, Dextromethorphan, Dimenhydrinate, Roxithromycin, Levocitrizine, Dicyclomine HCl, Norfloxacin, Ofloxacin, etc.
Amberlite IRP 88, Indion 234, Tulsion T – 335	Methacrylic acid DVB Polymer	-COOK	Weak cation	Ciprofloxacin, Chloroquine phosphate, Metronidazole, Azithromycin, Quinine sulphate

Table 3: Some Patents Related with Taste Masking Compositions (including ion exchange resins)

Patent no.	Title	Drug	Inventor, year
WO 2012/167878 A1	Edible oral strip or wafer dosage form containing ion exchange resin for taste masking	Ketoprofen	LI Michael H.C., Kurmm M., 2012 ¹⁷
WO2012/120522A1	A taste masked chewable tablet of sildenafil	Sildenafil	Murpani D., 2012 ¹⁸
WO2011/080683A1	Taste masked dosage forms of bitter tasting anti-retroviral drugs	Anti-retroviral	Kakumanu V. K., Isloor S., Arora, 2011 ¹⁹
WO2011/030351A2	Taste masked pharmaceutical compositions	Phosphodiesterase-5 (PDE-5) inhibitors	Pilgaonkar P., et al. 2011 ²⁰
US2011/0300224A1	Taste masked dosage form of pharmaceutically acceptable salt of escitalopram	Escitalopram	Murpani D., Pandora A. 2011 ²¹
US80088378B2	Taste-masked composition of cationic exchange resin	Active drug	Hargens R. D. et al 2011 ²²
WO2010/150221A1	Taste masked pharmaceutical compositions of pregabalin	Pregabalin	Huda I., et al. 2010 ²³
WO2009/074995A1	Taste masked chewable compositions of sildenafil citrate	Sildenafil citrate	Singh S., et al 2009 ²⁴
US2008/0044371A1	Taste-Masked Composition of Cationic Exchange Resin	Active drug	Hargens R. D. et al 2008 ²⁵
US 2008/0095842 A1	Rapidly Disintegrating Taste Masked Compositions and a Process for Its Preparations	Levocetirizine Dihydrochloride	Antarkar A. K., et al 2008 ²⁶
WO2007/146293A3	Improved composition and method for taste masking	Active drug	Becicka B. T., et al 2007 ²⁷
US 2006/0204559	Fast dissolving orally consumable films containing an ion exchange resin as a taste masking agent	Dextromethorphan	Bess W. S., et al 2001 ²⁸
US 2006/0115529	Fast melting tablets having taste-masking and sustained release properties	Active drug	Jeong S., et al 2006 ²⁹
US 2005/0036977	Taste masked resin ate and preparation thereof	Active drug	Gole D., et al 2005 ³⁰
WO2005/013934A2	Taste-masked composition of cationic exchange resin	Active drug	Hargens R. D. et al 2005 ³¹
US 6,565,877, B1	Taste masked compositions	Active drug	Mukherji G., et al 2003 ³²
US 6,514,492 B1	Taste masking of oral quinolone liquid preparations using ion exchange resins.	Quinolones	Gao R., et al 2003 ³³
WO01/70194A1	Fast dissolving orally consumable films containing an ion exchange resin as a taste masking agent	Dextromethorphan	Bess W. S., et al 2001 ³⁴
US 5032393	Drug adsorbates	Ranitidine	Douglas S. J., Bird F. R 1991 ³⁵
EP0212641	Taste masking compositions	Active amino or amido gp	Damani N. C., Tsau J. H. 1988 ³⁶

Table 4: Patented Work of Resinate for Sustained Release

Patent no.	Title	Drug / polymer	Inventor, year
US8414919	Sustained drug release composition	Cimetidine, ciprofloxacin / Amylose starch	Gervais S. et al, 2013 ⁴³
WO/2012/063257	Sustained release compositions	Active drug / resin	Pilgaonkar P. et al 2012 ⁴⁴
US 8337890	Modified release formulations containing drug-ion exchange resin complexes	Morphine, ibuprofen, codien/HPMC	Mehta K., Tu, Yu-hsing, 2012 ⁴⁵
US8062667	Modified release formulations containing drug-ion exchange resin complexes	Oxycodone, Albuterol Methylphenidate, Dextromethorphan / AMBERLITE™ IRP-69	Mehta K., Tu, Yu-hsing, 2011 ⁴⁶
US20110136921	Sustained Release Composition	Venlafaxine HCl, Diclofenac sodium / HPMC K100M	Dumbre N. T., et al 2011 ⁴⁷
WO/2010/127100	Compositions comprising an antihistamine, antitussive and decongestant in extended release formulations	Pseudoephedrine, Chlorpheniramine, Hydrocodone / Amberlite™ IRP69	Mcdermott J. Joseph et al, 2010 ⁴⁸
USP20080118570	Polymer coated drug-ion exchange resins and methods	chlorpheniramine polistirex, sodium polystyrene sulfonate Amberlite® IRP-69	Liu Z., et al., 2008 ⁴⁹
USP20070128269	Sustained drug release compositions	chloroquine and pyrimethamine/ HPMC K100M	Gervais S., et al, 2007 ⁵⁰
USP 20060263431	Opioid Sustained Release Formulation	Oxycodone, meperidine, methadone, nalbuphine, opium, pentazocine, propoxyphene/ styrene-divinylbenzene	Maloney A. M. ,2006 ⁵¹
USP 20050265955	Sustained release preparations	hydrocodone bitartrate / Dowex 50WX8H	Raman S. N. et al., 2005 ⁵²
WO/2003/020242	Sustained Release Preparations	dihydrocodeine phosphate, codeine phosphate, noscapine hydrochloride, phenylpropanolamine hydrochloride / Amberlite IR-120	Meadows D., et al, 2003 ⁵³
USP20020164373	Opioid Sustained Release Formulation	butorphanol, fentanyl, codeine, dihydrocodeine, hydrocodone bitartrate/ hydroxyalkylcellulose / styrene-divinylbenzene	Maloney A. M. ,2002 ⁵⁴
USP 6258350	Sustained release ophthalmic formulation	pilocarpine, epinephrine, etc. /poly (styrenedivinyl) benzene	Mallick S., 2001 ⁵⁵
USP5186930	Sustained Release oral Preparations	Phenylpropenolemine/styrene-divinylbenzene	Kogan P. W., et al, 1993 ⁵⁶
EP0429732	Sustained-release compositions containing cation exchange resins and polycarboxylic polymers	betaxolol, timolol, befunolol, etc. / Amberlite, Dowex	Jani R., Harris R. G., 1991 ⁵⁷

Disadvantages of Sustained Release Formulations

- 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 half-life, so diseased patients and significant patient's variation are not accommodated.
- Economic factors – more costly processes and equipments are involved.

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 resins 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 ions⁴¹.

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.

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-

- 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 resins of carboxylic acid. Hence, resins of strong cationic drugs are formulated as sustained release suspension, tablets, capsules and micro particles.

Evaluation of Drug Resonates

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

In vitro Evaluation

The *in vitro* test demonstrates the release pattern of a drug from resin 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 resin, 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.

In vivo Evaluation

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

Patents Related to Sustained Release Dosage Form with IER

US8414919

The invention relates to a sustained release formulation for delivering one or more pharmaceutically active agents. The formulation comprises cross-linked high amylose starch and at least one pharmaceutically active agent, and optionally can be subdivided into smaller dosage forms where the smaller dosage forms have substantially the same sustained release properties as the formulation from which they were derived. The formulations can provide sustained release for up to at least 24 h and because of their divisibility permits a recipient of the active agent or the person administering the active agent to titrate the dosage of the agent⁴³.

WO/2012/063257

Sustained release compositions comprising plurality of sustained release beads are disclosed. Particularly the sustained release beads comprise coated drug-resin complexes comprising drug-resin complexes of at least one active agent and at least one ion-exchange resin; coated with at least one release modifier⁴⁴.

US 8337890

A coated drug-ion exchange resin complex comprising a core composed of a drug complexed with a pharmaceutically acceptable ion-exchange resin is provided. The drug-ion exchange resin complex is in admixture with a release retardant. The coating is a polyvinyl acetate polymer and a plasticizer. Methods of making and products containing this coated complex are described⁴⁵.

US8062667

A coated drug-ion exchange resin complex comprising a core composed of a drug complexed with a pharmaceutically acceptable ion-exchange resin is provided. The drug-ion exchange resin complex is in admixture with a release retardant. The coating is a polyvinyl acetate polymer and a

plasticizer. Methods of making and products containing this coated complex are described⁴⁶.

US20110136921

A sustained release composition comprising spray dried particles of at least one polysaccharide gum and at least one polyhydric sugar alcohol, as well as methods of making the sustained released composition are provided. A sustained release pharmaceutical solid dosage form and a method of making the solid dosage form by compression are also provided⁴⁷.

WO/2010/127100

The invention provides oral formulations for the treatment of cold and allergy symptoms. Each formulation combines an antihistamine, an antitussive, and / or a decongestant into one extended release composition. The invention further provides for methods of making and using such formulations, as well as for methods for preventing abuse or extraction of a single drug present in an oral extended release composition comprising two or more of an antihistamine, antitussive, and / or decongestant⁴⁸.

US 20080118570

Included are compositions, and methods of making, coated controlled-release drug and ion exchange resin form complexes. Methacrylate coatings, which can be free of plasticizers particularly with Eudragit® NE type polymer, are preferred to enhance the control of drug release from the drug-resin complexes. Liquid formulations including the coated resin forms and a chelating agent to inhibit degradation are also included⁴⁹.

US 20070128269

The invention relates to a sustained release formulation for delivering one or more pharmaceutically active agents. The formulation comprises cross-linked high amylose starch and at least one pharmaceutically active agent, and optionally can be subdivided into smaller dosage forms where the smaller dosage forms have substantially the same sustained release properties as the formulation from which they were derived. The formulations can provide sustained release for up to at least 24 h and because of their divisibility permits a recipient of the active agent or the person administering the active agent to titrate the dosage of the agent⁵⁰.

US 20060263431 and USP20020164373

It includes a solid, oral, controlled release dosage form comprising a therapeutically effective amount of an opioid compound, or a salt thereof, a matrix-forming polymer and an ionic exchange resin^{51,54}.

US 20050265955

Disclosed sustained release drug particles suitable for forming sustained release oral pharmaceutical compositions. The sustained release drug particles comprise a drug-ion exchange resin complex and a water-permeable, diffusion barrier surrounding at least a portion of the drug-ion exchange resin complex. The diffusion barrier comprises a film-forming polymer and is free or contains no substantial traces of organic solvent. Also disclosed are oral pharmaceutical compositions, for example, oral suspensions, comprising the sustained release drug particles, a method for the controlled administration of a drug to a patient, and a method for manufacturing the sustained release drug

particles. The method of manufacturing involves the use of an aqueous coating composition comprising a water-permeable film-forming polymer such as ethylcellulose⁵².

WO/2003/020242

The invention relates to oral pharmaceutical preparations that comprise a pharmacologically active drug bound to small particles of an ion-exchange resin. Drug-resin complexes are coated with an aqueous based diffusion barrier comprising a water-permeable, film forming polymer that is relatively insoluble in gastrointestinal fluids thereby providing a controllable sustained release of drug under conditions encountered in the gastrointestinal tract. At least some of the barrier coated drug-resin particles may be coated with an enteric coating to provide a tailored release profile⁵³.

US 6258350

Sustained release formulations for topical ophthalmic administration are disclosed. The formulations comprise a basic active, a polyanionic polymer and a poly (styrenedivinyl) benzene cation exchange resin having a degree of cross-linking from about 4 to about 4.5 %⁵⁵.

US 5186930

Stable sustained release wax- and polymer-coated drug-ion exchange resin complexes especially useful in preparing oral suspensions are disclosed⁵⁶.

EP0429732

Disclosed are non stinging, sustained release ophthalmic formulations to control intraocular pressure in anti glaucoma therapy comprising a basic active, a cation exchange resin, and, inter alia, an acidic, mucomimetic polymer. Also disclosed are methods of treatment comprising administering such formulations topically to the eye when indicated for control and lowering for intraocular pressure⁵⁷.

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.

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