# Chapter 1

## INTRODUCTION

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Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
Chapter 1

INTRODUCTION

"Worst the taste of the medication, the better the cure" was once the prevailing attitude. Today this trend has changed and great importance is given to the organoleptic characteristics of pharmaceutical products i.e. mainly appearance, odor and taste. Masking of the unpleasant taste of a drug improves the compliance of the patient and product value.

More than 50% of the pharmaceutical products are administered orally for several reasons, of which better patient compliance and existence of highly developed technology are most important.

Oral administration of a drug having bitter and obnoxious taste with acceptable level of palatability is a challenge to the pharmacist in the present world, especially in pediatric and geriatric formulations. Thus, taste masking has become a potential tool in the present day pharmaceutical industry to improve patient compliance and commercial success of the product.

Taste masking is defined as 'a perceived reduction of an undesirable taste that would otherwise exist'.

The ideal solution to taste masking of bitter substances is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness. But up to date there is no single substance that acts as the universal inhibitor of bitter taste.

Recent years have seen a tremendous progress in the technique of masking the unacceptable taste of orally administered pharmaceuticals, such as conventional granulation, filling in capsules, coating with water insoluble polymers or pH dependent water soluble polymer, adsorption on ion-exchange resin, micro encapsulation with various polymers, complexing with cyclodextrin, chemical modification such as use of insoluble prodrugs, effervescent systems, salt formation, freeze drying process, multiple emulsions, liposomes and use of excipients like flavors, sweeteners, gelatin, gelatinized starch, lecithin like substances and surfactants.

Pharmaceutical companies are commercially motivated to invest time, money and resources in developing palatable, pleasant tasting products because good tasting products:...
Chapter 1 Introduction

? Enhance patient compliance
? Provide a competitive advantage when a therapeutic category is crowded with similar products e.g. anti-infective category etc.
? Provide brand recognition to combat private-label competition.

Aside from the commercially motivating factors to develop acceptable tasting products, the pharmaceutical industry is also motivated by the rules of regulatory agencies for pediatric drug products. Currently, a drug must comply with the Food and Drug Administration’s (FDA’s) campaign to improve labeling for pediatric products. The 23 FDA regulations, known as the Pediatric Rule, may mandate a drug firm to conduct pediatric clinical studies as part of the New Drug Applications.

In the pharmaceutical industry, taste-masking science broadly covers physiological and physiochemical approaches to prevent Active Pharmaceutical Ingredient (API) or drugs from interacting with taste buds; thereby eliminating or reducing negative sensory response. Physiological approaches consist of inhibiting or modifying an API-mediated bitterness response by incorporating agents into a pharmaceutical formulation. Agents like sodium chloride, phosphatidic acid and peppermint flavor are known to inhibit bitterness by selected API molecules via a mechanism that takes place at the bitterness receptors in the taste buds.

1.1 TASTE:

Taste is a survival mechanism, alerting us to potentially harmful or potentially nutritious substances. We process taste at three levels: the receptor level, the circuit level, and the perceptual level.

At the receptor level are approximately 10,000 chemoreceptors or taste buds, residing primarily on the tongue, with some delocalized receptors at the back of the throat. These receptors fall into five primary categories: bitter, sour, umani, salt, and sweet, with grouped receptors dissipated over the surface of the tongue for each stimulus.

‘Sweet’ signals carbohydrates or certain amino acids. ‘Sour’ characterizes vitamins. ‘Salt’ detects needed minerals. ‘Umani’ indicates protein and amino acids. In general, we experience these tastes as pleasant. Bitter sensation, however, is often unpleasant, suggesting alkaline water, alkaloid poisons, and spoiled foods.
APIs, of course, usually fit into the bitter category. Chemoreceptors for taste and olfaction (smell) respond to chemicals in an aqueous environment. Chemicals dissolved in saliva excite the taste receptors of the mouth, and airborne chemicals dissolved in epithelial mucus excite the olfactory receptors of the nose. The senses are complementary, with smell and taste working together to respond to, and more narrowly define, the same stimuli.

Taste depends on physiological and psychological factors. Physiological properties such as temperature and texture, clearly affect the perception of taste (consider the limited appeal of a cold cup of coffee). Human taste also appears to change with age. Many children dislike fresh vegetables; yet grow to enjoy them in adult life. Psychological factors can also influence taste perception: a childhood memory of badly formulated cough medicine can significantly modify taste perception of a modern formulation. Such factors underscore the role of taste in manufacturing a product that achieves patient compliance.

Regardless of the flavor system used, the challenge is how to deliver unpleasant compounds (APIs) while maintaining patient acceptability, efficacy, and compliance.

1.1.1 Anatomy and Physiology of Taste:

In mammal’s taste buds are aggregations of 30-100 individual elongated ‘neuroepithelial’ cells, which are often embedded in specialization of surrounding epithelium, termed ‘papillae’ (Figure 1.1A & 1.1B). At the apex of the taste bud, microvillar processes protrude through a small opening, the ‘taste pore’, into the oral milieu (Figure 1.1 C). At the base of the taste bud, afferent taste nerves invade the bud and ramify extensively, each fiber typically synapsing with multiple receptor cells within the taste bud.

*Location of taste buds*:

The taste buds are found on three types of papillae on the tongue,

1. A large number of taste buds are on the wall of the troughs that surrounds the circumvallated papillae, which forms a ‘v’ line on the posterior surface of the tongue.

2. Moderate numbers of taste buds are on fungi form papillae over the flat anterior surface of the tongue.
3. Moderate numbers are on the foliate papillae located in the folds along the lateral surface of the tongue.

4. Additional taste buds are located on the palate and few on the tonsillar pillars, the epiglottis and even in the proximal esophagus.

**Innervations of tongue:**

The receptor cell does not have axons. Transmitter relays information onto terminals of sensory fibers. Theses fibers arise from the ganglion cells of the cranial nerves VII (facial - branch called the chorda tympani) and IX (glossopharyngeal)

![Figure 1.1: Papillae and taste buds](image)

**Mechanism of stimulation of taste**:

The membrane of the taste cell, like that of other sensory receptor cells, is negatively charged on the side with respect to outside. Application of a taste substance to the taste buds causes partial loss of this negative potential- i.e. cell is depolarized. The decrease in potential, within the wide range, is approximately proportional to logarithm of concentration of stimulating substance. This change in the potential in the taste cell is the receptor potential for taste. The mechanism by which most stimulating substance react with the taste villi is by binding of the taste...
chemicals to the protein receptor molecule that protrude through the villus membrane. This in turn allows sodium to enter and depolarize the cell. Then the taste chemical is gradually washed away from the taste villus by saliva, which removes the stimulus.

1) Salt taste:

$\text{Na}^+$ ions enter the receptor cells via $\text{Na}$-channels. These are amilorid-sensitive $\text{Na}^+$ channels. The entry of $\text{Na}^+$ causes a depolarization, $\text{Ca}^+$ enters through voltage sensitive $\text{Ca}^+$ channels, transmitter release occurs and results in increased firing in the primary afferent nerve.

2) Sour taste:

Sour taste is acidic. $\text{H}^+$ ions block $\text{K}^+$ channels and are responsible for maintaining the cell membrane potential at hyperpolarized level. Blocking of these channels causes a depolarization; $\text{Ca}^+$ entry causes transmitter releases and increased firing in the primary afferent nerve.

3) Sweet taste:

There are receptors in the apical membrane that bind glucose (sucrose - a combination of glucose and fructose - and other carbohydrates). Binding to the receptor activates adenylyl cyclase, thereby elevating cAMP. This causes a PKA-mediated phosphorylation of $\text{K}^+$ channels, inhibiting them. Depolarization occurs $\text{Ca}^{2+}$ enters the cell through depolarization-activated $\text{Ca}^{2+}$ channels; transmitter is released increasing firing in the primary afferent nerve.

4) Bitter taste:

Bitter substances cause the second messenger ($\text{IP}_3$) mediated release of $\text{Ca}^{2+}$ from internal stores (external $\text{Ca}^{2+}$ is not required). The elevated $\text{Ca}^{2+}$ causes transmitter release and this increases the firing of the primary afferent nerve.

5) Umami taste:

Umami is the taste of certain amino acids (e.g. glutamate, aspartate and related compounds). Recently it has been shown that the metabotropic glutamate receptor (mGluR4) mediates umami taste.

Binding to the receptor activates a G-protein and this may elevate intracellular $\text{Ca}^{2+}$. Monosodium glutamate, added to many foods to enhance their taste (and the main ingredient of Soy sauce), may stimulate the umami receptors. But, in addition, there are ionotropic glutamate receptors (linked to ion channels),
i.e. the NMDA-receptor, on the tongue. When activated by these umami compounds (or soy sauce), non-selective cation channels open, thereby depolarizing the cell. Calcium enters, causing transmitter release and increased firing in the primary afferent nerve.

![Figure 1.2: Mechanism of taste perception](image)

1.2 TASTE ABATEMENT OF ORAL PHARMACEUTICALS:

The taste of any substance can be improved by two basic manipulations: either by reducing the drug solubility or by altering the ability of the drug to interact with taste receptors. The approaches below mentioned are primarily based on these two methods.

The principle approaches for bitter taste masking are:

1. Sensory approach
   a. Flavoring agents, Sweeteners and Amino Acids  
   b. Numbing taste buds

2. Chemical approach
   a. Prodrugs  
   b. Salt preparation

3. Barrier approach
   a. Viscosity modifier  
   b. Coating by Wet Granulation  
   c. Emulsions  
   d. Liposomes  
   e. Microspheres/Microcapsules

4. Complexation and adsorption
   a. Solid Dispersions  
   b. Adsorbate Formation  
   c. Complexation with ion exchange resins/polymers  
   d. Inclusion complex  
   e. Wax embedding
1.2.1 Sensory approach

I. Flavoring agents, Sweeteners and Amino Acid

It is important to understand that only soluble portion of the drug can generate the sensation of taste. Addition of flavors and sweeteners is the foremost and simplest approach for taste masking especially in case of pediatric formulations. This approach is, however, not very successful for highly bitter and highly water soluble drugs. Besides taste masking, this approach is also used to improve the aesthetic appeal of product, especially to make it more attractive.\(^25\)

In liquid formulations, water-soluble flavors are added to the aqueous component of a formulation, whereas poorly water-soluble flavors are added to the alcoholic or other non-bitter solvent component of the formulation. Fruit flavors are often used to mask sour taste, whereas bitter tasting drugs are often blended with salty, sweet or sour tasting agents. It is a well known fact that salty taste reduces sourness and increases sweetness, whereas sweet taste reduces bitterness. For example, fruity syrups such as raspberry and wild cherry syrups are often used to mask the excessive sour taste of a medicament. Cinnamon syrup has been used to mask excessive salty taste of drugs like ammonium chloride and other salts. Other syrups that have been used to accomplish the same task include orange syrup, lemon syrup\(^26\), etc. The perception of unpleasant organoleptic sensations such as bitterness or off taste initiated by volatile oils can be masked using agents such as fenchone and D-borneol in the amount undetectable by sensory organs\(^27\). High concentration of sugar or sugar derivatives have been used for taste masking the noxious and bitter taste of drugs, such as antitussive, antihistaminics, decongestants, and expectorants for use in liquid delivery systems\(^28,29\).

By combining amino acids, their salts, or a mixture of the two, it is possible to substantially reduce the bitter taste of drugs. Some of the preferred amino acids are sarcosine, alanine, taurine, glutamic acid, and glycine\(^30\).

II. Numbing of taste buds

Temporary numbing of taste buds by certain anesthetizing agents such as phenol and sodium phenolate has also been used to mask the unpleasant taste of drugs such as aspirin\(^31\). Swabbing of the gingiva in the oral cavity with a topical anesthetic has been shown to temporarily reduce the bitter taste of the dental anesthetics, which often leak into the oral cavity after an injection. Clove oil, has been found to be a...
good taste masking component for a number of medicinals because of its spicy and unaesthetic effect on taste buds. To support taste-masking capabilities of clove, vanilla flavor is preferred.

1.2.2 Chemical approaches

I. Prodrugs

Silyated compounds of erythromycin have markedly superior taste when compared to their corresponding parent compounds. It is believed that the silyated compounds of the antibiotics function as prodrugs releasing parent antibiotic in vivo. Clindamycin is an extremely bitter semi synthetic antibiotic. To improve its pharmaceutical acceptability, four clindamycin-2- acetyl esters of varying chain lengths, namely palmitate, laurate, hexanoate, and acetate were synthesized. The taste of palmitate ester is much better than the other esters.

II. Preparation of salts

In general, this approach is made to modify the solubility of the drugs. Sometimes the drugs are converted into particular salts to modify their taste. Megulunine, an acid addition salt of ibuprofen, increases not only solubility of ibuprofen but also provides significant taste masking effect. This salt form can be successfully incorporated into palatable formulation. Erythromycin can be made practically tasteless and odorless by preparing estolate salt. This is an attempt to modify the chemical composition of the drug substances so as to render it less soluble in saliva and thereby less stimulating for the taste buds, or to obtain as tasteless or less bitter form. Even if one is successful in preparing a new salt or a derivative of a bitter drug, the legalities of its new drug status from a regulatory point of view must be considered. Moreover, the solubility, stability, compatibility, and bioavailability aspects of the “new” compound must also be kept in mind.

1.2.3 Barrier approaches

I. Coating by Wet Granulation

This process may be described as one, which agglomerates drug particles through a combination of adhesion and cohesion using a wetting agent and binder. This method consists of mixing of the ingredients in a solids-liquids processor to form a dampened, agglomerated mass that may be then subdivided, dried, and sized.
to form a suitable free-flowing and compressible granulation. Although this process is primarily intended to impart flowability and compressibility to impalpable substances, under certain conditions it may be useful in the application of coatings to drug particles in order to mask or reduce their bitter taste. In general, this is the simplest approach to taste masking. Wet granulation may be accomplished with or without the inclusion of additional excipients such as lactose, sucrose, mannitol, sorbitol, other sugars, or starches.

Although this approach is similar to that for wet granulation of conventional tablets, some fundamental requirements should be kept in mind in selecting granulating /coating agent;

- Should form a flexible rather than a brittle film,
- Have no unpleasant taste or odor,
- Be insoluble in saliva but not interfere with drug dissolution.

Disintegrants should preferably be included in the wet granulation to ensure proper dissolution of the granules. Such granules can also be prepared by use of fluidized bed or air suspension coating technique, which may provide an efficient coating in comparison to classical wet granulation technique.

Although taste improvement by coating is attractive in its simplicity, it should be understood that this method might suffice only for mildly to moderately unpleasant tasting drugs.

II. Viscosity modifier

In this technique, aqueous dispersions of natural gums such as acacia, tragacanth, xanthan, etc. or semisynthetic/synthetic polymers such as sodium carboxy methyl cellulose, polyethylene glycols, hydroxy propyl methyl cellulose, hydroxy propyl cellulose, etc are used to increase the viscosity, which limits the contact of unpleasant tasting drugs with taste buds. Acetaminophen suspensions can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. Combination of polyethylene glycol and sodium carboxy methylcellulose were used to mask the unpleasant taste of drugs such as pseudoephedrine HCl, dextromethorphan etc. A syrup composition comprising Phenobarbital or acetaminophen in a polyhydric alcohol such as polyethylene glycol or polypropylene glycol with polyvinyl pyrrolidone, gum arabic, gelatin was used to mask bitter taste.
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III. Emulsions

The single as well as multiple emulsions are helpful in masking the taste of medicament. The use of multiple emulsions for masking the bitter taste of chloroquine was investigated in O/W/O and W/O/W emulsion systems. The results indicated that the O/W/O systems could mask the taste of chloroquine to some extent. Mineral oil is used as a lubricating cathartic, and has an unpleasant taste when taken orally. The formulation of O/W type of emulsion markedly improves its palatability.

IV. Lipid vesicles

Another way of masking the unpleasant taste of drugs is to entrap them into lipid vesicles or liposomes. Incorporating them into liposome prepared with egg phosphatidyl choline can mask the bitter taste of an antimalarial drug, chloroquine phosphate.

V. Microcapsules / Microspheres

Microcapsulation involves coating of drug particles using a natural or synthetic polymer or wax. Several techniques such as coacervation separation, solvent evaporation, spray drying, spray congealing, fluidized bed coating, etc. have been used. Encapsulating in the mixture of gelatin and acrylic polymers such as eudragit L-100, S-100, and E-100 masked the unpleasant taste of the clarithromycin. Such encapsulated drugs can be successfully formulated as a suspension. James et al.\textsuperscript{14} masked the bitter taste of Cefuroxime axetil by coating with lipids which get disperse on contact with gastrointestinal fluid.

1.2.4 Complexation and adsorption

I. Solid Dispersions

Bad-tasting drugs can be prevented from stimulating taste buds by adsorption onto substrates capable of keeping drugs adsorbed while in the mouth but releasing them eventually in the stomach or gastrointestinal tract. Adsorbing on magnesium silicate as a substrate can mask the taste of the dextromethorphan hydrobromide. Such method can be applied with various substrates such as Bentonite, Veegum, and Silica.

II. Adsorbate Formation

Drug-substrate adsorbate can be prepared by two methods; Solvent method and Melting method.
Solvent Method:

Generally the formation of an adsorbate involves dissolving the drug in a solvent, mixing the solution with the substrate, and evaporating the solvent, leaving the drug molecules adsorbed upon the substrate. The variables of the process, such as choice of solvent, substrate, proportions, mixing conditions, rate of evaporation, and temperature, must be optimized to give the desired product.

Melting Method:

In this method, the drug/s and a carrier are melted together by heating. The melted mixture is then cooled and rapidly solidified in an ice bath with vigorous stirring. The product is then pulverized and sized. Heat labile drugs, volatile drugs and drugs that decompose on melting are unsuitable for this method. The method is simple with low cost and no problem of residual solvents as encountered in the solvent evaporation method.

**III. Inclusion Complexation**

In the inclusion complex formation, the drug molecule (guest molecule) fits into the cavity of complexing agent (host molecule) forming a stable complex. The complex is capable of masking the bitter taste of the drug by decreasing the amount of particles exposed to the taste buds and/or by decreasing the drug solubility on ingestion, both activities leading to decreasing bitterness of the drug. The forces involved in inclusion complexes are usually of the van der Waals type, and one of the most widely used complexing agents in inclusion type complexes is B - cyclodextrin, a sweet, nontoxic, cyclic oligosaccharide obtained from starch. Three primary methods have been reported for the preparation of cyclodextrin inclusion compounds.

1. Equimolar quantities, or a 10-fold excess of water-soluble substances, are dissolved directly in concentrated hot or cold aqueous solution of the cyclodextrin. The inclusion compounds crystallize out immediately or upon slow cooling and evaporation.

2. Water insoluble drugs are dissolved in a non-water-miscible organic solvent and shaken with a concentrated aqueous solution of cyclodextrins. The inclusion compounds crystallize at the interface between the layers, or as precipitate. The crystals must then be washed with solvent to remove uncomplexed drug and dried under appropriate conditions to remove residual solvents.
3. The drug substance is added to the cyclodextrin and water to form slurry, which undergoes an increase in viscosity with continuous mixing. This may concentrate to a paste that can be dried, powdered, and washed.

1.3 ION EXCHANGE RESINS:
1.3.1 Introduction and Historical Review

Seldom does one encounter a phenomenon that finds many applications in such widely divergent fields such as agriculture, biology, medicine and chemistry. In recent years ion exchange has shown itself to be in such position.

The treatment of waters by solid adsorbents such as sand is probably as ancient as civilization itself. Records from ancient time indicate that sand filters were used for the purification of sea and impure drinking waters. Appreciations of the various relationships involved in this phenomenon have come about gradually, and the subject has interested scientific people throughout the ages.

In Sylva Sylvarum, Bacon wrote “...to have read that trial hath been made of salt water passed through earth through ten vessels, one within another, and yet it hath lost its saltness as to become potable, but when drained through twenty vessels hath become fresh” Apparently Bacon had visualized the operation of deionisation centuries before such an operation actually materialized. Later Hales described experiments that indicated that seawater was freed of salts on passing through stone cisterns. The ability of clays and soils to adsorb components to manure liquors was extensively studied by Sir Humphry Davy, Lambuschini, Huxtable, and others in the early part of the nineteenth century. Gazzari in 1819 also observed that clay decolorized liquid manure and adsorbed soluble substances that were gradually released to soils. Liebig, and Thompson, found that clays had the ability to adsorb ammonia.

Although Fuechs, in 1833, reported that certain clays released potassium and sodium when treated with lime, the credit for the recognition of the phenomenon of ion exchange is generally attributed to Thompson and Way, two English agricultural chemists.

In 1848 H.S. Thompson reported to J. Thomas Way that, on treating a soil with either ammonium sulphate or ammonium carbonate most of the ammonia was absorbed and lime was released. In the years 1850 to 1854, Way reported the results
of his extensive study of this phenomenon before the Royal Agriculture Society of London.

Ways' works represent the first systematic study of ion exchange, and no further contributions were found towards an understanding of this reaction for several decades.

However, although credit is given to Way and Thompson for the recognition of the ion exchange reaction, it is quite interesting to note that Graham, the father of colloid chemistry, had reported two decades earlier that carbon was able to adsorb the silver from silver nitrate, and Esprit had found that a neutral salt upon contact with carbon liberated acidity when the cation of the salt was absorbed.

Although the exchange of ions that is encountered on contacting a soluble electrolyte with some ionic solid was evident in work prior to Way's classic work, his experiments served as a stimulus to many scientists of his time and many who followed. Boedeker, Petres, Wolfs, Frank, Sestini and Eichorn extensively continued Ways' work. In 1876, Lemberg found that it was possible to transfer the mineral leucite ($\text{K}_2\text{O}.\text{Al}_2\text{O}_3.\text{4SiO}_2$) into analcime ($\text{Na}_2\text{O}.\text{Al}_2\text{O}_3.\text{4SiO}_2.\text{2H}_2\text{O}$) by leaching the mineral with a solution of sodium chloride and that the transformation could be reversed by treating analcime with solution of leucite. These experiments of Lembergs are a classic milestone in that they illustrate clearly the stoichiometry and the reversibility of the process of ion exchange.

Although the work done by Way and Lemberg stimulated many soil chemists and geochemists, it was not until the beginning of nineteenth century that ion exchange became a unit of operation on an industrial scale for water softening. The classic ion exchange studies of Gans are probably the first worthwhile attempts to utilize ion exchange for industrial purposes. Gans employed both natural and synthetic aluminium silicates for softening waters and also for treating sugar solutions. The turn of the century also inaugurated an avalanche of contributions to the nature of the ion exchange phenomena in clays, soils and other silicates. However, it was not until the work of Pauling and Bragg on the crystal structure of the micas and clays and the subsequent work by these had been done on the relationship between ion exchange and crystal structure that there was a much clearer understanding of ion exchange.
The limitations of siliceous ion exchangers became more and more evident as commercial exploitation of these substances was attempted, and it was because these limitations were recognized that those heralded the discovery of sulfonated coal cation exchangers and the work of Adams and Holmes engaged in the field of ion exchange.

Adams and Holmes synthesized the first ion exchange resins in 1935 for their potential use in purification and separation. In the beginning, this was significant only in the field of agricultural and organic analytical chemistry, which later attracted research by healthcare professionals into this subject. From 1950's to the present the Complexation and release of drugs with ion-exchange materials have been studied extensively.

The advantage of ion-exchange materials for taste masking is their ability to bind and exchange charged drug molecules. In general, for taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of the drug. Sometimes strong cation exchange resins are also used for taste masking purpose. 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 be broken down in the acidic environment of the stomach.

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In the past few years, IER have been extensively studied in the development of novel drug delivery systems and other biomedical applications. Several ion exchange resin products for oral and peroral administration have been developed for immediate release and sustained release purposes. Research over last few years has revealed that IER are equally suitable for drug delivery technologies, including controlled release, transdermal, buccal, site specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical, and taste masking.

1.3.2 Structure and Classification of Ion Exchange Resin:

Ion exchange resins are polymeric particles (or gels) that contain basic or acidic groups, which can form ionic complexes with oppositely charged drugs. The
resins are insoluble solids that are not absorbed by the body; hence, they do not have significant associated side effects.

Ion exchange resins can be classified based on the nature of the structural and functional components and ion exchange process. A general classification of ion exchangers is given in Figure 1.3.

![Figure 1.3: Classification of Ion Exchange Resins](image)

**Figure 1.3:** Classification of Ion Exchange Resins
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The most important class of ion-exchangers is the organic ion-exchange resins. They consist of a framework, a so called matrix, carrying a functional component having a positive or negative electric fixed charge, which is compensated by mobile counter ions of opposite sign. A small amount of mobile ions of the same sign (co ions) can also be present. The framework is typically a hydrophobic hydrocarbon chain. Ionic groups in the framework are such as –SO₃ --, –COO --, –PO₃ --, –AsO₃ -- in cation-exchangers and –NH₃ +, –NH₂ +, –NH + and –S + in anion-exchangers.

Table 1.1: Classification of Ion Exchange Resins

<table>
<thead>
<tr>
<th>Type of resin</th>
<th>Polymeric backbone</th>
<th>Usual form</th>
<th>Pharmacopoeial name</th>
<th>Trade names</th>
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<tbody>
<tr>
<td>Strong cation exchange resin</td>
<td>Styrene and divinyl benzene copolymer</td>
<td>-SO₃ Na⁺</td>
<td>Sodium polystyrene sulphonate USP₃⁷</td>
<td>Tulsion-344, Amberlite IRP 69, Indion- 254</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-SO₃ H⁺</td>
<td>-</td>
<td>Dowex 50, Tulsion-343, Indion-224</td>
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<tr>
<td>Weak cation exchange resin</td>
<td>Acrylic acid and divinyl benzene copolymer</td>
<td>-COOH⁺</td>
<td>Polacrilex</td>
<td>Tulsion-335, Amberlite IRP 64, Indion- 204</td>
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<td></td>
<td>-COOK⁺</td>
<td>Polacrillin USP₃⁷</td>
<td>Tulsion-339, Amberlite IRP 88, Indion- 294</td>
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<tr>
<td>Strong anion exchange resin</td>
<td>Styrene and divinyl benzene copolymer</td>
<td>-N⁺(R)₃Cl⁻</td>
<td>Cholestyramine USP₃⁷</td>
<td>Duolite AP 143, Amberlite IR 400, Indion- 454</td>
</tr>
<tr>
<td>Weak anion exchange resin</td>
<td>Acrylic acid and divinyl benzene copolymer</td>
<td>-N⁺(R)₂Cl⁻</td>
<td>-</td>
<td>Dowex 2, Amberlite IRP 45</td>
</tr>
</tbody>
</table>
Framework in pharmaceutical grade IER consists mostly of polyacrylic acid or polystyrene cross linked with suitable amount of cross linking agent such as divinyl benzene, amount of which greatly affects swelling property and, in turn, rate of ion exchange and capacity to adsorb large molecules. Depending on grafted ionic groups in framework, IER can be classified as weak or strong cation/anion exchangers. Cation exchange resins can be used in the hydrogen form (H-form) or in the salt form (Na-form). In the former case the Hydrogen ions- and in the latter, the metal ions-of the ionogenic groups of the sorbent exchange for the cations of the dissolved electrolyte.

Anion-exchange resins can be used in the form of bases or salts.

The content of ionogenic groups in the resin is determined by potentiometric titration. Different ionogenic groups give different shapes of the curves for pH versus content of NaOH or HCl in the solution.

Types of resin along with exchange species, polymer backbone, pharmacopoeial and trade names is shown in Table 1.1

1.3.3 Properties of Ion Exchange Resins

1. **Particle size:** The rate of ion exchange reactions depends on the size of resin particles. Decreasing the size significantly decreases the time required for the reaction to reach equilibrium with surrounding medium. IERs are available in wide size range from 2 to 3 mm spherical beads to powder as fine as few microns.

2. **Porosity and swelling:** Porosity is defined as the ratio of the volume of the material to its mass. The limiting size of ions that can penetrate into the resin matrix depends strongly on the porosity, which depends mainly on the amount of cross-linking agent, and also on polymerization process. Swelling is directly proportional to number of hydrophilic functional groups and inversely proportional to degree of cross-linking.

3. **Cross-linking:** Percentage of cross-linking affects purely physical structures of resin particles. Resins with low cross-linking can swell into structure that is soft and gelatinous when take up water, while resins with high cross linkage are somewhat hard and brittle.

4. **Available capacity:** The capacity of an ion exchanger is a quantitative measure of its ability to take up counter ions and is therefore of major importance. This depends mainly on accessibility of the drug to the site of exchange.
5. Acid base strength: Resin containing Sulphonic, phosphoric or carboxylic acid exchange groups have approximate pKa values of <1, 2-3, 4-6 respectively. Anionic exchangers are quaternary, tertiary or secondary ammonium groups having apparent pKa values of >13, 7-9 and 5-9 respectively. Acid base strength is significant for the reason that the strength of bond and subsequent rate of release of drug depends on this strength; also the pH environment needed for loading and release of drug can be predicted.

6. Selectivity of resin for counter ion: Since ion exchange involves electrostatic forces, selectivity mainly depends on relative charge, and ionic radius of hydrated ions competing for an exchange site and to some extent on Hydrophobicity of competitor ion.

7. Stability: The IERs are remarkably inert substances. They are resistant to attack by chemicals and heat to large extent. The limitation is degradation in presence of strong gamma rays.

8. Toxicity: The resins are insoluble solids that are not absorbed by the body; hence, they do not have significant associated side effects or toxicity. However, commercial products can’t be used as obtained as they contain impurities that can cause toxicity. Therefore, careful purification of resins is required prior to treatment with drugs.

9. Exchange capacity and Equilibrium phenomenon:

The principal properties of these resins are their exchange capacity to exchange its insoluble ions with those in solution. Soluble ions may be removed from the solution through exchange with the counter ions adsorbed on the resin as illustrated in this equation:

\[
\text{Re-} \text{SO}_3^- \text{Na}^+ + \text{drug}^+ \rightarrow \text{Re-} \text{SO}_3^- \text{drug}^+ + \text{Na}^+
\]

\[
\text{Re-N} (\text{CH}_3)_3^+ \text{Cl}^- + \text{drug}^- \rightarrow \text{Re-N} (\text{CH}_3)_3^+ \text{drug}^- + \text{Cl}^-
\]

These are equilibrium reactions in which extent of exchange is governed by the relative affinity of the resin for particular ions. Relative affinity between ions may be expressed as a selective coefficient derived from the mass action expression given below.

\[
K_{DM} = \frac{[D]_r [M]_s}{[D]_s [M]_r}
\]
Where,

\[ [D]_r = \text{drug concentration in resin}, \quad [M]_s = \text{counter ion concentration in the solution}. \]

\[ [D]_s = \text{drug concentration in the solution}, \quad [M]_r = \text{counter ion concentration in resin}. \]

The exchange capacity refers to number of ionic sites per unit weight of or volume of ion exchange resin (meq. per gram). The weight basis value (meq. per gram) is generally much higher than the volume based exchange capacity since the wet resin is highly hydrated. The exchange capacity may limit the amount of drug that may be absorbed on a resin and hence the potency of a complex. Carboxylic acid resins are derived from the acrylic acid polymer and have higher exchange capacities (about 10 meq. per gram) than Sulphonic acid (about 4 meq. per gram) or amine resins because of bulkier ionic substitute and polystyrene matrix. Therefore, higher drug percentage may often be achieved with carboxylic acid resins.

1.3.4 How to select a suitable Ion Exchange Resin:

The selection of IER for dmg delivery applications is primarily governed by the functional-group properties of the ion exchange resin. However, the following points need to be considered during selection:

- Capacity of the IER [i.e. the concentration of the exchangeable group in the resin, usually expressed in mill equivalents per gram (meq/gm) of dry resin].
- Degree of cross linking in the resin matrix
- Particle size of resin
- Nature of drug and site of drug delivery. It is also important to evaluate the resin in the pH- and ionic-strength environment, simulating the in vivo situation
- Swelling ratio
- Biocompatibility and biodegradability
- Regulatory status of the ion exchange resin

For example, a low degree of cross linking of the resin will facilitate the exchange of large ions, but it will also cause volume changes in the resin upon conversion from one form to another. Similarly, the use of a strong IER will give a rapid rate of exchange, but it could also cause hydrolysis of the labile drugs because strong ion exchange resins are effective acid-base catalysts. Therefore, a fine balance of all the parameters needs to be made to achieve optimal performance of drug-delivery systems containing ion exchange resin.
1.3.5 Theory of ion exchange

Ion exchange is a stoichiometric process in which any counter ions that leave the ion exchanger are replaced by an equivalent amount of other counter ions. This is a consequence of the electro neutrality requirement. The ion exchange is essentially a diffusional process, but also has relation to chemical reaction kinetics. Usually the ion exchangers are selective, they take up some counter ions in preference to others. The rate-determining step in ion exchange is diffusion either within the ion-exchanger itself or in the diffusion boundary layer. Rechenberg proposed that at low concentration of counter ion, the rate of exchange is controlled by film diffusion, and at high concentrations by particle diffusion. The equilibrium distribution of the drug species between the resin and external solution phases results from both electrostatic and hydrophobic interactions. In the ion exchange resins the ions are known to bind to the ion-exchanger by two mechanisms. The first layer of molecules is bound strongly via electrostatic bonds. These strong bonds have a chemical nature and only ionized molecules are capable to be bound to this layer, where the concentration of binding molecules is very high. The molecules bind to the second layer via loose interactions of hydrophobic nature (Figure 1.4)

![Image](image_url)

**Figure 1.4:** Interaction between drug and resin

The hydrophobic interactions may also occur between the side chains of bound molecules. Both the ionized and non-ionized molecules will be present in the second layer.

The process of ion exchange depends on many factors that include:
1. pKa of drug and resin
2. pH of loading and eluting medium
3. Hydrophobicity of drug
4. Temperature of medium
5. Ionic strength of eluting medium
6. Concentration of drug in loading solution
7. Resin properties like particle size and crosslinking

Drug release from Drug: resin complex (Resinate) depends upon two factors:
1. The ionic environment (i.e. pH and electrolyte concentration) within the gastrointestinal tract.
2. The properties of resin.

Figure 1.5: Factors that affect IER process involved in the delivery of cationic drug.

Drug molecules attached to the resins are released by appropriate charged ions in the gastrointestinal tract, followed by diffusion of free drug molecules out of the resin as shown below.

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

Where X and Y are ions in the gastrointestinal tract.

If drug resin complex is administered orally, a small amount of drug may be released in saliva followed by significant and continuous release in stomach where drug is exposed to high acid and chloride concentration.
In contrast, drugs bound to weakly acidic or basic groups on IER are released much more readily in stomach

\[
\text{Re-COO}^- - \text{drug}^+ + \text{H}^+ \quad \leftrightarrow \quad \text{Re-COO}^- - \text{H}^+ + \text{drug}^+
\]

The process of exchange between the electrolyte ion and the mobile sorbent ion passes through the following stages:\(^\text{43}\):

1. Movement of the displacing ion from the bulk of solution to the sorbent surface;
2. Movement of the displacing ion inside the sorbent to the point of exchange;
3. Chemical exchange reaction, i.e., the ion exchange reaction proper;
4. Movement of the displaced ion inside the sorbent from the point of exchange to its surface;
5. Movement of the displaced ion from the sorbent surface into the bulk of the solution.

The kinetics of these processes is determined by the value of the diffusivities of ions, and this is connected with their dimensions and the resistance of a medium. The magnitude of sorption and the capacity of the ionite depend on the affinity of the ion for a resin, the density of a network, the degree of swelling and porosity of the ionite\(^\text{43}\).

1.3.6 Preparation Of Resinate:

In practice, drug in an ionic form (usually in solution) is mixed with the appropriate IER to form a complex, known as ‘resinate’. The performance of resinate is governed by several factors, such as:

- The pH and temperature of the drug solution
- The molecular weight and charge intensity of the drug and ion exchange resin
- Geometry
- Mixing speed
- Ionic strength of the drug solution
- Degree of cross linking and particle size of the ion exchange resin

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
The nature of solvent

Contact time between the drug species and the ion exchange resin

Once the selection of resin is made the next step involves preparation of its complex with drug. Following steps are involved in the preparation of resinate:

1. Purification of resin by washing with ethanol and water.
2. Changing of ionic form of IER might occasionally be required to convert resin from one form to another, if it doesn't have desired counter ions. Na$^+$ form of resin can be converted to H$^+$ by soaking the resin with HCl.

Preparation of resinate is normally done by two processes

1. Batch process
2. Column process

Figure 1.6: Flow Diagram for drug: resin complex preparation by Batch and Column process

1. Batch process:

   This is usually the preferred method due to its ease of operation. This process involves slurring of the drug and resin in water, filtering or decanting the liquid on the top, slurring the resin with desired acid, base or salt solution to change cycle (if necessary), decanting and washing with water several times, and treating with the appropriate drug solution. After complexation the complex formed is washed with water and dried.
The drug: resin complexation process depends on several factors, which can affect the percent complexation of drug with resin, which are:

- Effect of mixing time and swelling time on Complexation
- Effect of Activation of ion exchange resin
- Effect of pH
- Effect of Temperature
- Effect of Mode of mixing
- Effect of concentration of loading solution

![Diagram](image)

**Figure 1.7:** Different factors affecting batch and column Processes

2. **Column process:**

   In typical column procedure for preparing adsorbate of an amine drug on a strong cation exchange resin, the resin is slurried in water. The slurry is 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 removed from the column, filtered by vacuum, and oven dried. An analogous procedure can be used to adsorb a carboxylated drug on ion exchange resin, using NaOH to convert the resin to basic cycle.

1.3.7 **Evaluation of drug resinate preparations:**

   1. **In vitro tests:**

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
In vitro dissolution testing is an important tool in the proper control and evaluation of drug resinate preparations. Various methods have been described in the literature. Despite attempts to develop a standard method, no such dissolution procedure has as yet been accepted. Commonly employed methods to test drug resinate include the on-column and batch exposure of the resinate to simulated gastric juice and intestinal fluids (U.S.P-XV; enzymes are often omitted to make the chemical analysis easier). Both methods differ in their boundary conditions. Batch experiments are carried out with the solutions of finite volumes, whereas for on column elution the infinite solution volume condition is closely approached. Kressman, Boyd et al. and Dickel and Meyer discussed typical apparatus needed for studying dissolution from ion exchange resins. Comparison of the results from different research groups is sometimes difficult because the variables of the in vitro test methods, such as sampling times, agitation, fluid composition, etc., are largely different or incompletely described.

2. Kinetic interpretation of in vitro dissolution tests:

The rate of release of drug molecules from ion exchange resins can be influenced by various factors. On the one hand, release kinetics depend on the resins inherent properties, such as the type of ionogenic groups, cross-linking density and particle size, and on the other hand, on the nature of the drug itself and the test conditions, e.g., ionic strength of the dissolution medium. Since the surrounding ionic environment affects complexation and decomplexation, in our present study we have carried out release study in simulated salivary fluid and simulated gastric fluid.

To compare the in vitro dissolution results it would be convenient to characterize the release data by a representative physical constant. Quantitative studies of ion exchange processes have been mainly concerned with equilibria rather than with kinetics. This is understandable since most studies dealt with the exchange of small ions, in which case equilibrium is reached fairly rapidly. For large organic ions the equilibrium is reached only very slowly and kinetics considerations are important. In the exchange process one counter ion must migrate from the solution into the interior of the ion exchanger, while another one must migrate from the exchanger into the solution. The rate-controlling step was shown by Boyd et al. to be diffusion either in the resin particle itself or in an adherent stagnant film. As
particle and film diffusions are sequential steps, the slower of the two is rate controlling. Another possible rate controlling step may be the chemical exchange reaction. However, this could never be demonstrated conclusively. It has been found that the release process of ionic drug ions from resinates eluted with simulated gastric or intestinal fluid is controlled mostly by particle diffusion.

Particle diffusion controlled- Assuming that all resin particle are uniform sphere of radius \( r \), Boyd, Adamson, and Meyers\(^5\) showed that, under conditions where particle diffusion is the rate controlling step, the fraction of drug release \( (F) \) as function of time is given by:

\[
F = 
\frac{Q_t}{Q_x} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{e^{-n^2t}}{n^2} \quad \text{..........................(1)}
\]

Where, \( Q_t \) and \( Q_x \) are the amounts released at time \( t \), and the time \( \infty \), respectively, and

\[ B = \left[ \frac{2D}{r^2} \right], \quad D \] being the effective diffusion coefficient of the exchanging ions in the resin particles. Equation 1 holds only for conditions of infinite solution volume, obtained when solution of constant composition is continuously passed through a thin layer of beads, or in a batch experiment if the solution volume is very large. For \( F \)-values lower than 0.85 and after Fourier transformation and integration, Reichenberg\(^4\) obtained the following equation

\[
F = \frac{6}{\pi^2} \sqrt{Bt} - \frac{3}{\pi^2} Bt + \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{e^{-n^2t}}{n^2} \quad \text{..........................(2)}
\]

Since only the first two terms need to be considered, for each experimental \( F \)-value the corresponding \( Bt \)-value is given by

\[
Bt = 2 \left[ 1 - \frac{1}{3} \frac{F}{F_0} \right] - 2 \left[ \frac{1}{3} \left( 1 - \frac{1}{3} \frac{F}{F_0} \right)^{\frac{3}{2}} \right] \quad \text{..........................(3)}
\]

By plotting the \( Bt \) values against time, a straight line passing through the origin with the slope equal to \( B \) should be obtained. From these \( B \)-values the effective diffusion coefficient \( D \) can be calculated. Since \( dF/dt \) is proportional to \( B \) and \( B \) is inversely proportional to the square of the particle radius, the rate of exchange will be inversely proportional to the square of the particle radius. The \( D \) value calculated in
this way is a representative physical characteristic to describe the release behavior of resinates under standardized conditions. Resinates have been characterized by means of their B or D value by N.C. Chaudhary, Gyselinck, and Schacht. Motycka and Nairn studied the release behavior of resinate beads coated by several encapsulation techniques. They found that the encapsulating film slowed the rate of release, but the release data still gave linear Bt-t plots.

3. In vivo procedures:

In vitro experiments are valuable in the evaluation of potential slow release formulations. However, the data must be treated with great caution because they have significance only when an in vitro-in vivo correlation can be established. In vivo experiments with animals are very helpful in screening the dosage forms but are no substitute for human trials. Direct measurements of the duration of the desired therapeutic response is unquestionably the best method for evaluating the properties of long acting dosage forms. Unfortunately, few drugs can be directly evaluated in humans. Moreover, the response cannot be measured quantitatively or subjected to statistical treatment. In vivo procedure used for estimating drug activity of resinate include serum concentration level determination, urinary excretion and toxicity studies. Blood concentration level determinations have been used frequently. However, the disadvantage is that for many drugs, doses exceeding the therapeutic dose are frequently applied to facilitate chemical analysis. As an alternative measure of the physiological availability of the drugs, urinary excretion has been proposed by Campbell and co-workers. For certain drugs a direct relationship has been shown between excretion rate and the plasma concentrations. Since the clinical response of many drugs is based on their concentration in the blood stream, it would appear that a valid relation exists between clinical tests and the amount of drug excreted in the urine.

Toxicity studies on animals have also been used for demonstrating the duration of an effect in vivo. Becker and Swift noted that the median lethal dose (LD50) and the median time of death (LT50) if compared with the pure drugs, were significantly increased with the resinate forms. A close correlation between the delay in the time of death and the urinary excretion rate has been reported. The method appears to be useful for studying resinate formulations of relatively toxic drugs.
However, differences in responses can also be due to lack of bioavailability and not exclusively to the prolonged effect.

1.3.8 IER: Applications in drug delivery research

IERs provide the formulator with a versatile tool for wide range of applications. The use of IER in pharmaceuticals can be summarized under following heads:

1. Taste masking:

Certain drugs that have very bitter taste; can be made relatively tasteless by adsorbing the drug on IER. Although all the IERs can be useful for this purpose, the proper selection depends on ionic character of drug and release characteristics. Weak cation exchangers are most preferable for their ability to remain undissociated at salivary pH, and thus masking the taste of bound drug and further releasing it rapidly at acidic pH of stomach. Ion exchange materials have been used for taste masking by a number of workers. Borodkin and Yunker reduced the bitterness of dextromethorphan, ephedrine, and pseudoephedrine using polymethacrylic acid cation exchange resins. Avari and Bhalekar reported taste masking of highly bitter antibiotic, sparfloxacin with Indion 204 weak cation exchanger. Pisal et al. have used an Indion 234 weak cation exchanger for taste masking of ciprofloxacin. Bajaj et al. formulated the oral controlled release brohexine HCl suspension using strong cation exchange resin. A summary of literature survey of drug resin complexes used for taste masking purpose is given in Table 1.2
Table 1.2: Literature survey of drug resin complexes used for taste masking

<table>
<thead>
<tr>
<th>Drug-IER pKa</th>
<th>Ion exchange resin</th>
<th>Type</th>
<th>Functional group</th>
<th>Ionic form</th>
<th>pKa</th>
<th>Particle size</th>
<th>Ratio Drug: Resin</th>
<th>Percent Complex</th>
<th>Process</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol HCl: Dowex-50wx8</td>
<td>9.45</td>
<td>Strong polystyrene/DVB</td>
<td>SO3^-</td>
<td>Na^+</td>
<td>&lt;1</td>
<td>300-20 μm</td>
<td>1:2</td>
<td>18.7</td>
<td>Batch</td>
<td>W.J.Irwin et al DDIP 13(9-11), 1987</td>
</tr>
<tr>
<td>Propranolol HCl: Amberlite</td>
<td>9.45</td>
<td>Weak Methacryllic acid/DVB</td>
<td>COO^-</td>
<td>H^+</td>
<td>4-6</td>
<td>75-40 μm</td>
<td>1:2</td>
<td>29.9</td>
<td>Batch</td>
<td>W.J.Irwin et al DDIP 13(9-11), 1987</td>
</tr>
<tr>
<td>Ibuprofen: Dowex X-200</td>
<td>-</td>
<td>Anionic exchange resin with DVB</td>
<td>SO3^-</td>
<td>-</td>
<td>75-150 μm</td>
<td>1:1</td>
<td>37.4</td>
<td>Column</td>
<td>W.J.Irwin et al DDIP 16(6), 1990</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen: cholestyramine</td>
<td>-</td>
<td>Strong Anionic exchange resin with DVB</td>
<td>SO3^-</td>
<td>-</td>
<td>38-63 μm</td>
<td>1:1</td>
<td>25.9</td>
<td>Batch</td>
<td>W.J.Irwin et al DDIP 16 (6), 1990</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen: Dowex X-200</td>
<td>-</td>
<td>Anionic exchange resin with DVB</td>
<td>SO3^-</td>
<td>-</td>
<td>75-150 μm</td>
<td>1:1</td>
<td>40.5</td>
<td>Column</td>
<td>W.J.Irwin et al DDIP 16 (6), 1990</td>
<td></td>
</tr>
<tr>
<td>Mefanamic acid: cholestyramine</td>
<td>-</td>
<td>Strong Anionic exchange resin with DVB</td>
<td>SO3^-</td>
<td>-</td>
<td>38-63 μm</td>
<td>1:1</td>
<td>45</td>
<td>Batch</td>
<td>W.J.Irwin et al DDIP 16 (6), 1990</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen: cholestyramine</td>
<td>-</td>
<td>Strong Anionic exchange resin with DVB</td>
<td>SO3^-</td>
<td>-</td>
<td>38-63 μm</td>
<td>1:1</td>
<td>28.9</td>
<td>Batch</td>
<td>W.J.Irwin et al DDIP 16 (6), 1990</td>
<td></td>
</tr>
<tr>
<td>Propranolol HCl: Amberlite IRP69</td>
<td>9.45</td>
<td>Strong styrene/DVB</td>
<td>SO3^-</td>
<td>Na^+</td>
<td>&lt;1</td>
<td>(150-20 μm)</td>
<td>-</td>
<td>45</td>
<td>Column</td>
<td>Akkaramongkonpran et al</td>
</tr>
</tbody>
</table>

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
### Table 1.1: Ion Exchange Resin Data

<table>
<thead>
<tr>
<th>Drug-IER pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Ion Exchange Resin</th>
<th>Type</th>
<th>Functional group name</th>
<th>Ionic form</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Particle size</th>
<th>Ratios Drug: Resin</th>
<th>% Complex</th>
<th>Complex process</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromhexine HCl:Indion-244</td>
<td>-</td>
<td>Strong/ polystyrene matrix</td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;⁻</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>32-144 μm</td>
<td>1:1</td>
<td>50</td>
<td>Batch</td>
<td>Ulviya S. et al&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dextrometh orphan: Dowex-50w</td>
<td>8.3</td>
<td>Strong polystyrene/DVB</td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;⁻</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>100-200 mesh dry (150-75 μm)</td>
<td>-</td>
<td>43.3</td>
<td>Batch</td>
<td>T. Pongjanyakul et al&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dextrometh orphan: Amberlite IR P69</td>
<td>8.3</td>
<td>Strong polystyrene/DVB</td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;⁻</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>100-500 mesh wet (150-20 μm)</td>
<td>-</td>
<td>32.9</td>
<td>Batch</td>
<td>T. Pongjanyakul et al&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ranitidine: Indion-234</td>
<td>8.2</td>
<td>Weak polyacrylic</td>
<td>COO⁻</td>
<td>K&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>65-75 μm</td>
<td>1:2</td>
<td>36.48</td>
<td>Batch</td>
<td>Bhalekar et al Int.J.Pharm.Exp. p.70</td>
</tr>
<tr>
<td>Ciprofloxacin: Indion-234</td>
<td>8.8</td>
<td>Weak polyacrylic</td>
<td>COO⁻</td>
<td>K&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>54 μm</td>
<td>1:1.3</td>
<td>96.50</td>
<td>Batch</td>
<td>Pisal et al&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rizatriptan benzoate: Indion 204</td>
<td></td>
<td>Weak polyacrylic</td>
<td>COO⁻</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>150 μm</td>
<td>1:1</td>
<td>64.10</td>
<td>Batch</td>
<td>P.D.Chaudhary et al&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rizatriptan benzoate: Indion 214</td>
<td></td>
<td>Weak polyacrylic</td>
<td>COO⁻</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>150 μm</td>
<td>1:2</td>
<td>96.07</td>
<td>Batch</td>
<td>P.D.Chaudhary etal&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rizatriptan benzoate: Tulsion-335</td>
<td></td>
<td>Weak methacrylic</td>
<td>COO⁻</td>
<td>H&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>&lt;150 μm</td>
<td>1:1</td>
<td>71.25</td>
<td>Batch</td>
<td>P.D.Chaudhary etal&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rizatriptan benzoate: Tulsion-339</td>
<td></td>
<td>Weak methacrylic</td>
<td>COO⁻</td>
<td>K&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>&lt;150 μm</td>
<td>1:1</td>
<td>78.26</td>
<td>Batch</td>
<td>P.D.Chaudhary etal&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>CPM: Tulsion-344</td>
<td>9.2</td>
<td>Strong polystyrene/DVB</td>
<td>SO&lt;sub&gt;3&lt;/sub&gt;⁻</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>80-150 μm</td>
<td>1:3</td>
<td>-</td>
<td>Batch</td>
<td>Paradkar etal</td>
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<tr>
<td>Quinine sulphate: Indion-234</td>
<td>8.5</td>
<td>Weak acrylic copolymer</td>
<td>COO⁻</td>
<td>K&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-6</td>
<td>65-75 μm</td>
<td>1:5</td>
<td>99.1</td>
<td>Batch</td>
<td>V.B.Patravale etal&lt;sup&gt;72&lt;/sup&gt;</td>
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</tbody>
</table>

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
<table>
<thead>
<tr>
<th>Drug-IER pka</th>
<th>Ion exchange resin</th>
<th>Type</th>
<th>Functional group</th>
<th>Ionic form</th>
<th>pH</th>
<th>Particle size</th>
<th>Ratios Drug: resin</th>
<th>Percentage Complex</th>
<th>Completion process</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine sulphate: Indion-254</td>
<td>8.5</td>
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<td>Na⁺</td>
<td>&lt;1</td>
<td>65-75 µm</td>
<td>1:5</td>
<td>-</td>
<td>Batch</td>
<td>V.B.Patra vale et al 72</td>
</tr>
<tr>
<td>CPM: Amberlite CG-50R</td>
<td>9.2</td>
<td>Weak polycrylic</td>
<td>COO⁻</td>
<td>H⁺</td>
<td>4-6</td>
<td>-</td>
<td>1:2</td>
<td>73</td>
<td>Batch</td>
<td>O.L.Spro ckel et al 73</td>
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<tr>
<td>CPM: Amberlite CG-120R</td>
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<td>Strong DVB</td>
<td>SO₃⁻</td>
<td>H⁺</td>
<td>&lt;1</td>
<td>-</td>
<td>1:2</td>
<td>99</td>
<td>Batch</td>
<td>O.L.Spro ckel et al 73</td>
</tr>
<tr>
<td>Roxithromycin: Indion 204</td>
<td>-</td>
<td>Weak polycrylic</td>
<td>COO⁻</td>
<td>H⁺</td>
<td>4-6</td>
<td>150 µm</td>
<td>1:5</td>
<td>Good</td>
<td>Batch</td>
<td>P.D.Amin et al 24</td>
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<tr>
<td>Roxithromycin: Indion 214</td>
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<td>COO⁻</td>
<td>H⁺</td>
<td>4-6</td>
<td>150 µm</td>
<td>1:5</td>
<td>Good</td>
<td>Batch</td>
<td>P.D.Amin et al 24</td>
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<td>Chloroquine phosphate:</td>
<td>8.4</td>
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<td>H⁺</td>
<td>4-6</td>
<td>72-147 µ</td>
<td>1:2</td>
<td>Upto 98</td>
<td>Batch</td>
<td>Agrawal et al 9</td>
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<tr>
<td>Cinchonidine sulphate: Dowex-50w</td>
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<td>SO₃⁻</td>
<td>NH₄⁺</td>
<td>&lt;1</td>
<td>50-100 µm</td>
<td>-</td>
<td>69.6</td>
<td>Column</td>
<td>Vyas bhatt et al jps 75</td>
</tr>
<tr>
<td>Cinchonidine sulphate: Amberlite-200</td>
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<td>Strong styrene DVB</td>
<td>SO₃⁻</td>
<td>NH₄⁺</td>
<td>&lt;1</td>
<td>20-50 µm</td>
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<td>Column</td>
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<td>Strong styrene DVB</td>
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<td>NH₄⁺</td>
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<td>20-50 µm</td>
<td>-</td>
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<tr>
<td>Sumatriptan succinate: Tulsion-335</td>
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<td>COO⁻</td>
<td>H⁺</td>
<td>4-6</td>
<td>&lt;150 µm</td>
<td>-</td>
<td>99.25</td>
<td>Batch</td>
<td>Sohi et al 3</td>
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<td>Ranitidine HCl: Indion-234</td>
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<td>COO⁻</td>
<td>K⁺</td>
<td>4-6</td>
<td>65-75 µm</td>
<td>1:2</td>
<td>36.48</td>
<td>Batch</td>
<td>Bhalekar et al 65</td>
</tr>
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</table>

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
<table>
<thead>
<tr>
<th>Drug-IER pKa</th>
<th>Ion exchange resin</th>
<th>Type</th>
<th>Functional group</th>
<th>Ionic form</th>
<th>pK a</th>
<th>Particle size</th>
<th>Ratios Drug: resin</th>
<th>Percent Complex</th>
<th>Comple x process</th>
<th>Refere nce</th>
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</thead>
<tbody>
<tr>
<td>Ephedrine HCl: IndionCRP-254 9.5</td>
<td>Strong polystyrene/DVB</td>
<td>SO3^- Na^+</td>
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<td>100-500 BSS</td>
<td>-</td>
<td>0.574</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td></td>
</tr>
<tr>
<td>Ephedrine HCl: IndionCRP-244 9.5</td>
<td>Strong polystyrene matrix</td>
<td>SO3^- H^+</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
<td>0.765</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td></td>
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<tr>
<td>Ephedrine HCl: AmberliteIRP69 9.5</td>
<td>Strong polystyrene/DVB</td>
<td>SO3^- Na^+</td>
<td>&lt;1</td>
<td>(150-20 μm)</td>
<td>-</td>
<td>0.685</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td>Diphenhydramine HCl: IndionCRP-254 -</td>
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<td>SO3^- Na^+</td>
<td>&lt;1</td>
<td>100-500 BSS</td>
<td>-</td>
<td>0.971</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td>&lt;1</td>
<td>-</td>
<td>-</td>
<td>1.098</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td></td>
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<td>(150-20 μm)</td>
<td>-</td>
<td>1.004</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td>Strong polystyrene/DVB</td>
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<td>100-500 BSS</td>
<td>-</td>
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<td>S.P.Manek et al 76</td>
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<td>CPM: IndionCRP-244 9.2</td>
<td>Strong polystyrene matrix</td>
<td>SO3^- H^+</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
<td>0.681</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
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<td></td>
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<tr>
<td>CPM: AmberliteIRP69 9.2</td>
<td>Strong polystyrene/DVB</td>
<td>SO3^- Na^+</td>
<td>&lt;1</td>
<td>(150-20 μm)</td>
<td>-</td>
<td>0.726</td>
<td>Column</td>
<td>S.P.Manek et al 76</td>
<td></td>
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<tr>
<td>Methapyrilene HCl -</td>
<td>Weak poly methacrylic acid</td>
<td>COO^- H^+</td>
<td>4-6</td>
<td>72-147 μm</td>
<td>1.12: 1</td>
<td>99.9</td>
<td>Column</td>
<td>Borodkin S. et al 60(10) 1971 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
## Chapter 1

### Introduction

<table>
<thead>
<tr>
<th>Drug-IER pKα</th>
<th><strong>Ion exchange resin</strong></th>
<th><strong>Type</strong></th>
<th><strong>Functional group</strong></th>
<th><strong>Ionic form</strong></th>
<th><strong>pKα</strong></th>
<th><strong>Particle size</strong></th>
<th><strong>Ratios Drug: resin</strong></th>
<th><strong>Percent Complex</strong></th>
<th><strong>Process</strong></th>
<th><strong>ref</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>9.5</td>
<td>Weak</td>
<td>poly methacrylic acid</td>
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<td>4-6</td>
<td>72-147 μm</td>
<td>1.89:1</td>
<td>96.3</td>
<td>Column</td>
<td>Borodkin S. etal 1971</td>
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<tr>
<td>Pseudo Ephedrine HCl</td>
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<td>Weak</td>
<td>poly methacrylic acid</td>
<td>COO⁻ H⁺</td>
<td>4-6</td>
<td>72-147 μm</td>
<td>3.97:1</td>
<td>37.9</td>
<td>Column</td>
<td>Borodkin S. etal 1971</td>
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<tr>
<td>Ephedrine: AmberliteIRP88</td>
<td>9.5</td>
<td>Weak</td>
<td>methacrylic with DVB</td>
<td>COO⁻ K⁺</td>
<td>4-6</td>
<td>100-500 mesh</td>
<td>-</td>
<td>80.7</td>
<td>Batch</td>
<td>Borodkin S. etal 1970</td>
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<tr>
<td>Pseudo Ephedrine: AmberliteIRP88</td>
<td>9.7</td>
<td>Weak</td>
<td>methacrylic with DVB</td>
<td>COO⁻ K⁺</td>
<td>4-6</td>
<td>100-500 mesh</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Borodkin S. etal 1970</td>
</tr>
<tr>
<td>Carbinoxamine maleate: AmberliteIRP88</td>
<td>8.1</td>
<td>Weak</td>
<td>methacrylicDVB</td>
<td>COO⁻ K⁺</td>
<td>4-6</td>
<td>100-500 mesh</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Borodkin S. etal 1970</td>
</tr>
<tr>
<td>X1 resin</td>
<td>X= relative degree of cross linking (% nominal DVB)</td>
<td>Strong</td>
<td>polystyrene/ DVB</td>
<td>SO₃⁻ H⁺</td>
<td>&lt;1</td>
<td>0.215 mm</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Kanhere S.S etal 1968</td>
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<tr>
<td>X2 resin</td>
<td>-</td>
<td>Strong</td>
<td>polystyrene/ DVB</td>
<td>SO₃⁻ H⁺</td>
<td>&lt;1</td>
<td>0.215 mm</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Kanhere S.S etal 1968</td>
</tr>
<tr>
<td>X4 resin</td>
<td>-</td>
<td>Strong</td>
<td>polystyrene/ DVB</td>
<td>SO₃⁻ H⁺</td>
<td>&lt;1</td>
<td>0.215 mm</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Kanhere S.S etal 1968</td>
</tr>
<tr>
<td>X4 resin</td>
<td>-</td>
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<td>polystyrene/ DVB</td>
<td>SO₃⁻ K⁺</td>
<td>&lt;1</td>
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<tr>
<td>X4 resin</td>
<td>-</td>
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<td>polystyrene/ DVB</td>
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<td>&lt;1</td>
<td>0.66 mm</td>
<td>-</td>
<td>-</td>
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<tr>
<td>X8 resin</td>
<td>-</td>
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<td>polystyrene/ DVB</td>
<td>SO₃⁻ H⁺</td>
<td>&lt;1</td>
<td>0.215 mm</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Kanhere S.S etal 1968</td>
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<tr>
<td>X12 resin</td>
<td>-</td>
<td>Strong</td>
<td>polystyrene/ DVB</td>
<td>SO₃⁻ H⁺</td>
<td>&lt;1</td>
<td>0.215 mm</td>
<td>-</td>
<td>-</td>
<td>Batch</td>
<td>Kanhere S.S etal 1968</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Resin Name</th>
<th>Resin Type</th>
<th>Counterions</th>
<th>Particle Size</th>
<th>Batch No.</th>
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<tr>
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<td>H⁺</td>
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<td>X20 resin</td>
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<td>SO₃⁻</td>
<td>H⁺</td>
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<td>IR120</td>
<td>Strong polystyrene/DVB</td>
<td>SO₃⁻</td>
<td>H⁺</td>
<td>&lt; 1</td>
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<tr>
<td>Amberlite IR200</td>
<td>Strong polystyrene/DVB</td>
<td>SO₃⁻</td>
<td>H⁺</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Amberlite IR200</td>
<td>Strong polystyrene/DVB</td>
<td>SO₃⁻</td>
<td>K⁺</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Amberlite IR200</td>
<td>Strong polystyrene/DVB</td>
<td>SO₃⁻</td>
<td>Na⁺</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>AM15</td>
<td>Strong polystyrene/DVB</td>
<td>SO₃⁻</td>
<td>H⁺</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

2. Tablet disintegration: In order to ensure the drug release from dosage form, it is desirable that it disintegrates uniformly and quickly. IER can be used for tablet disintegration. This is due to the fact that resins swell significantly once it imbibes moisture. Since the resin in potassium form swells much more than resin in hydrogen form, Potassium form of resin "Polacrillin Potassium" is preferred in this application. It has been reported that the tablets formulated with Polacrillin potassium a have tendency to disintegrate faster with increased hardness.

The advantages of ion exchange resins as tablet disintegrants over conventional ones are,

1. The rate of penetration of water and the subsequent swelling are very fast and this cuts down the disintegration time substantially.
2. The ion exchange resins swell on getting hydrated but do not dissolve or have an adhesive tendency, a feature commonly encountered with gums.
3. Ion exchange acts as a disintegrant even at a very low concentration, thus reducing the size of tablet.

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4. Ion exchange resins facilitate the compression phase by conferring greater hardness to the tablet.

5. Ion exchange resin works equally efficiently with hydrophilic and hydrophobic drugs, especially with the latter where the conventional disintegrants are ineffective.

3. **Drug stabilization:** Vitamin B12 deteriorates on storage. This necessitates addition of overages. The stability of Vitamin B12 can be prolonged by complexing it with a weak cation exchange resin. This complex has been reported to be as effective as free form of vitamin.

4. **Sustained release:** The release of Drugs from IER depends upon a series of ionic interactions between various body fluids and drug: resin complex referred as ‘Resinate’. Strong exchangers are particularly suitable for this application. Various sustained release dosage forms have been developed using ion exchange resins. These include
   
   * Oral suspensions
   * Transdermal drug delivery
   * Nasal and ophthalmic drug delivery
   * Topical drug delivery
   * Parenteral drug delivery

5. **Targeted drug delivery:**

   In the recent few years, considerable work has been done in the field of drug targeting. IERs also have drawn attention from the research works owing to their ability to remain in stomach for considerable period of time. The mechanism is mucosal and epithelial adhesion, and thus retention is less affected by mucous turnover. Additional advantage is that such prolonged gastric retention and uniform distribution are not influenced by dose size and fed state. Site-specific delivery of doxorubicin in cancer treatment has also been developed with minimum side effects and increased effectiveness.

6. **Therapeutic applications:**

   Some IERs are useful also as active ingredients. A strong exchanger, Cholestyramine is used as bile sequestering agent and thus acts as anti hyperlipidemic agent. This resin has also been complexed with antihyperlipidemic drugs like Gemfibrozil for the same treatment. Cation exchangers are useful for potassium...
reduction. In addition to the utility of ion exchange resins as excipients, these materials are being explored for their therapeutic potential as well. Cholestyramine was the first polymeric resin-based drug that was approved for the treatment of high cholesterol. The cationic resin in this case serves as a sequestrant to bind bile acids in the gastrointestinal tract. The binding and effective removal of bile acids forces the liver to consume cholesterol to synthesize more bile acids. This leads to the indirect reduction in cholesterol levels. The advantage of this therapy was that it did not use conventional drugs, and hence had lower side effects as compared to conventional therapies (e.g., Welchol developed by Genzyme). Specificity for these resins has been achieved by the use of polymers that bind not only via electrostatic interactions but also other forces, such as hydrophobic interactions. Cationic resins have also been used as oral therapeutics to reduce phosphate levels for end stage renal disease patients (e.g., Renagel developed by Genzyme).^1

7. Recent Advances:

In last few years, fairly new applications for IER have been noticed. Avari and Bhailekar^6^ reported improved dissolution of sparfloxacin bound to weak cation exchanger. They reported faster dissolution of this poorly soluble drug bound to weak cation exchanger, Indion 204, as compared to marketed formulation. Rohm and Haas claim certain new uses of IER. These uses include reduction in deliquescence and hygroscopicity and polymorphism^7^8. Drugs which form crystalline solids often can exist in more than one crystal form, each of which may have distinct properties in terms of solubility, melting point etc. Invariably, one crystal form may be more active or easier to handle than another although the conditions under which the various crystal forms appears may be so close as to be every difficult to control on the large scale. In some cases, one crystal form can be transformed into another on storage and this can cause problems with the effectiveness of the formulation. This effect is known as polymorphism and is of increasing concern to the pharmaceutical industry. By loading drugs onto functional polymers, many of the problems associated with polymorphs can be eliminated to give reliable, consistent drug properties. Some API's are extremely sensitive to moisture in the environment, to such an extent that if left in contact with moist air for even short periods of time, crystalline materials turn into problematical paste or even liquids. Typically, the Pharmaceutical industry has sought to control this effect by using very tight environmental controls in their

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manufacturing and formulation areas. Loading an API onto a functional polymer imparts some of the characteristics of the polymer onto the resulting resinate, in particular, the physical properties of a fine free flowing powder. It has been shown that the amount of moisture uptake by the API is significantly reduced and even at elevated moisture uptakes, resinate remains a free flowing powder which is easily formulated.

1.4 RAPIDLY DISINTEGRATING TABLETS:

Among the dosage form developed to facilitate ease of medication, the rapid dissolving / disintegrating tablet (RDT) is one of the most widely employed forms as commercial products\(^2\). The RDT has remarkable disintegration property; without water it rapidly disintegrate in the mouth within few seconds. When RDT is placed in oral cavity, saliva quickly penetrates into the pores causing rapid disintegration.

Rapid disintegrating tablet is known by various names like mouth dissolving tablet; Mouth disintegrating tablet; Orodispersible tablet; Rapidly melting tablet; rapid dissolving tablet; Quick disintegrating tablet; Quick dissolving tablet; etc. Various workers use all these terms synonymously. The ultimate objective behind formulating all these dosage forms is disintegration within 60 seconds.

The targeted populations for rapid disintegrating tablet dosage form,

A) The patients such as pediatric, geriatric, bedridden or developmentally disabled who may face difficulty in administering conventional tablets, capsules and oral liquids or syrup. Most of the time such inconvenience of administration results in high incidence of noncompliance and ineffective therapy.

B) The patients who have active life style.

C) When local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores or teething.

D) To deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablet /capsule.

E) For mentally ill patients.

RDTs also provides advantages over other dosage forms such as Dispersible / Effervescent tablet, Chewing gums, and Chewable tablets, which are commonly used to enhance patient compliance. Effervescent or Dispersible tablets require preparatory steps before administration. The elderly who often are unable to chew large pieces of
gum or tablets, sometimes experience unpleasant taste when bitter drugs are present. In this case, the bitterness of chewable tablet markedly increases because of the prolonged time that they are in the mouth or as a result of leaching of the drug from chewed or broken microcapsules.

The advantages of RDTs are being recognized increasingly in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term orodispersible tablet as a “tablet to be placed in the mouth where it dispersed rapidly before swallowing”.

1.4.1 Salient features of rapid disintegrating drug delivery system are:

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric and psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form.
- Good mouth feel property of rapid disintegrating tablet helps to change the basic view of medication as “bitter pill”, particularly for pediatric patients.
- Rapid dissolution of drug and absorption, which may produce rapid onset of action.
- Pregastric absorption can result in improved bioavailability; this will help in reduction of doses and will improve clinical performance.
- It combines advantages of both, tablet as well as liquid orals while also offering advantages over both traditional dosage forms.

In the market, some of the drugs are available in oral liquid forms for the patients who have difficulty in swallowing conventional tablets and capsules. As oral liquids have good taste, color and flavor, patients easily accept these dosage forms. But oral liquids frequently face the problems of physical, chemical and biological instability. Also special packages are required which are not easily portable. The main problem associated with liquid orals is dose nonuniformity, as the patient has to measure his/her own medication using a teaspoon, tablespoon, or other suitable measuring device.

RDT is one of best alternatives to oral liquids and extemporaneously prepared formulations. As oral liquids, RDTs have a good taste, color and flavor and hence they have good patient compliance. Since RDT is a unit solid dosage form, it is easily

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Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.
portable and also the prescriber will have flexibility in prescribing dosage. In addition to this, RDT does not pose so many problems of physical, chemical and biological stability as those of oral liquids. Thus, better palatability and exact dosing will result in better patient compliance and effective therapy.

**Desired criteria for formulating Rapid disintegrating tablet dosage form**

Rapid disintegrating tablet should;

- Disintegrate in the mouth within few seconds,
- Not have objectionable taste and/or odor,
- Have a pleasant mouth feel,
- Leave minimal or no residue in the mouth after administration,
- Be portable without fragility,
- Exhibit low sensitivity to environmental conditions such as humidity and temperature,
- Allow manufacturing using conventional processing and packaging equipments.

### 1.4.2 Technologies for formulation of Rapid Disintegrating Tablets

The fast disintegrating / dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, basic approaches to developing RDT include maximizing the porous structure, incorporating appropriate disintegrating agent, and using highly water-soluble excipients in the formulation.

Various technologies used in the manufacturing of RDTs include,

- Freeze-drying or lyophilization
- Tablet molding
- Direct compression
- Sublimation
- Spray drying
- Cotton candy process
Freeze-drying or lyophilization:

Freeze-drying is a process in which water is sublimated from the product after freezing. The lyophilized form offers more rapid dissolution than other available solid products. This technique forms a basis of Zydis, Quicksolv, and Lyoc technologies, which are used to manufacture RDTs.

R.P. Scherer patented Zydis technology by employing freeze-drying process for the preparation of mouth dissolving tablet on the basis of patents issued to Gregory et al.

The lyophilization process imparts glossy amorphous structure to the bulking agent and sometimes to the drug, thereby enhancing the dissolution characteristics of the formulation.

Manufacturing of RDT using lyophilization technique involves series of steps. First, the active drug is dissolved or dispersed in an aqueous solution of carrier. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The tray holding the blister packs is passed through a liquid nitrogen ‘freezing tunnel’ to freeze the drug solution/dispersion. Then, the frozen blister packs are placed in the refrigerated cabinets to continue the freezing process, and they are subjected to freeze-drying. After freeze-drying, the aluminum foil backing is applied on a blister sealing machine. The use of lyophilization is limited due to high cost of the equipment. Other major disadvantage of the final dosage form includes lack of physical resistance in standard blister packs and, therefore, special packaging is required.

Tablet molding:

Tablet produced by molding are solid dispersions. Flash tab, Orasolv, Durasolv and WOW tab are developed on the basis of molding technology.

Molded tablet can be prepared using different techniques; compression molding, heat molding and no-vacuum lyophilization. In compression molding, tablets are prepared using water-soluble additives. All ingredients are passed through fine mesh, dry blended, wetted with hydro alcoholic solvents and then compressed into tablet using low compression forces. The solvent present inside is removed by air-drying. The so formed molded tablets have a porous structure, which enhances dissolution.
Molded tablet prepared using heat-molding process involves setting the molten mass that contains a dispersed drug. This process uses agar solution as a binder and blister packaging well as a mold to manufacture tablet. The process involves preparing a suspension of drug, agar, and sugar (e.g. Mannitol, lactose), pouring the suspension into the blister packaging well, allowing the agar solution to solidify at room temperature to form a jelly, and drying it at 30°C under vacuum. No-vacuum lyophilization is another reported process to prepare molded tablet. This involves evaporation of a solvent from a drug solution at standard pressure.

Pebely et al. evaporated a frozen mixture containing gum (e.g. acacia, caragenan, guar, tragacanth, etc), a carbohydrate (e.g. maltodextrin, dextrose, mannitol, lactose, etc.), and a solvent in a tablet shaped mold. As the molded tablets contain water-soluble ingredients, the tablet dissolves completely and rapidly. The active ingredient in most cases is absorbed through the mucosal lining of the mouth. Compared to lyophilization, tablets produced by molding technique are easier to scale up to industrial manufacture. Tablet prepared using molding technique frequently faces a problem of low mechanical strength. Hence to improve the mechanical strength, binding agents like sucrose, polyvinyl pyrrolidone, cellulose polymer like hydroxypropyl methylcellulose may be added to the solvent system.

**Direct compression:**

Direct compression is the convenient and most cost effective technique of tablet manufacturing, as conventional equipment and limited number of processing steps are involved in it. The disintegration and/or solubilization pattern of RDT prepared by direct compression technique depends on single or combined action of disintegrant/s, water-soluble excipients and/or effervescent agent. Disintegration time of tablet varies inversely with size of tablet. Disintegrants have major role in the disintegration and dissolution process of RDT made by direct compression. To ensure high disintegration rate; choice of suitable type and an optimal amount of disintegrant are important. Below the optimal concentration, disintegration time will be more and above the optimal concentration disintegration time will remain approximately constant or even increase. Disintegrant efficacy is strongly affected by size and hardness of tablet. Disintegration efficiency is based on force equivalent concept, which is the combined measurement of swelling force development and amount of...
water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force.

After giving a water treatment to the agar powder, it was used as a disintegrant for MDT by Kuchekar et al\(^5\).

Amin et al prepared a taste-masked mouth dissolving tablets of Roxithromycin. They used Eudragit E100 and a weak cation exchange resin for taste masking of roxythromycin\(^6\).

Dandagi et al had prepared taste masked mouth disintegrating Ofloxacin tablet. They used a sweetener (aspartame) and a polymer (Eudragit E100) for taste masking of ofloxacin\(^6\).

Patel et al. evaluated various superdisintegrants viz. croscarmellose sodium, crospovidone, and sodium starch glycolate, for disintegrating ability in various ratios. Crospovidone was found to be the most effective superdisintegrant giving lowest disintegration and wetting times\(^7\).

Wadhwani and Amin developed a mouth-dissolving tablet of taste-masked Roxithromycin. They had masked the taste of drug by granulation with Eudragit NE 30D and Eudragit E100 along with flavors and sweeteners\(^6\).

Shirwarkar and Ramesh had formulated a fast disintegrating tablet of atenolol by dry granulation method. They studied croscarmellose sodium, crospovidone, and sodium starch glycolate in their formulations. From their studies they concluded the optimized concentration for croscarmellose sodium and sodium starch glycolate as 8%w/w whereas 10%w/w for crospovidone for rapid disintegration of tablet. They also reported croscarmellose sodium as the best superdisintegrant among the three used\(^8\).

Redkar et al. reported D-Solv technology for the preparation of rapid disintegrating tablet of bitter drugs\(^9\).

Kaushik et al. formulated a mouth dissolving formulation of Olanzepin by effervescent technique. They concluded that sodium bicarbonate and citric acid in the ratio of 10:8 is optimum for producing soothing fizz and excellent palatability in oral cavity\(^10\).

Nayak and Gopalkumar formulated fast dissolving tablets of Promethazine theoclate using three different techniques; effervescent melt technique, superdisintegrant addition, and melt technology. They observed that the tablet
prepared by effervescent melt technique was better in terms of disintegration and drug release\textsuperscript{101}.

Dash et al. developed a rapidly disintegrating calcium carbonate tablet by direct compression method and compared this tablet with commercially available effervescent calcium carbonate tablet. They concluded that tablet prepared by direct compression disintegrates more rapidly than the effervescent formulation\textsuperscript{102}.

A patent had been granted to Top Laboratories for an effervescent preparation of glycine based low dosage aspirin tablet\textsuperscript{103}.

The main drawback of effervescent excipients is their hygroscopicity. Hence, their manufacture requires control of humidity conditions and protection of the final product. Another approach to manufacturing MDT by direct compression is the use of sugar-based excipients e.g. dextrose, fructose, lactitol, maltitol, mannitol, sorbitol, starch hydrolysate, polydextrose, xylitol, etc., which display high aqueous solubility and sweetness.

Mizumoto et al. have classified sugar-based excipients into two types on the basis of their moldability and dissolution rate\textsuperscript{104}. Type I saccharides e.g. lactose and mannitol exhibit low moldability but a high dissolution rate. Type II saccharides e.g. maltose and maltitol exhibit high moldability but a low dissolution rate. Moldability in this respect is defined as the capacity of compound to be compressed and to dissolve and does not refer to the formation of a true molding by melting or solvent wetting. The moldability of a type I sugar can be improved by granulating it with a type II saccharide solution.

\textit{Sublimation:}

The presence of porous structure in the tablet matrix is the key factor for rapid disintegration of MDT. The basic principle involved in the preparation of MDT by sublimation technique involves incorporation of volatile material to the tablet formulation and the compression of well-mixed blend into the tablet, followed by volatilizing the volatile material from the tablet. Removal of volatile material creates pores in the tablet and these pores will help in rapid disintegration of the tablet.

Volatile materials such as ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylene tetramine, naphthalene, urea, urethane, etc.
can be used to prepare porous tablet of good mechanical strength. Water can also be used as pore forming material for preparation of highly porous RDT\textsuperscript{100, 105,106}.

Kusum Devi et al. formulated a mouth-dissolving tablet of Domperidone using a sublimation technique. They tried ammonium carbonate and camphor as a sublimating agent at 10-40\% concentration\textsuperscript{107}.

Adel M. Aly et al. examined the effects of superdisintegrants (Kollidone CL, Ac-Di-Sol, and Primojel) on dissolution and absorption of tenoxicam from solid dispersion formulation. The Primojel formulation had the highest drug absorption level, which was improved by tableting via camphor sublimation\textsuperscript{108}.

\textit{Spray drying:}

Spray drying is a process by which highly porous powder can be produced. Allen et al. reported spray drying technique for preparing mouth-dissolving tablet\textsuperscript{109, 110,111}. The formulations that were produced contained hydrolyzed and unhydrolysed gelatin as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrant. Adding effervescent base further enhanced disintegration and dissolution. The formulation was spray dried to yield a porous powder. Tablets produced from this powder disintegrate within 20 seconds in aqueous medium.

\textit{Cotton Candy Process:}

Cotton candy process is also known as candyfloss process. This technique forms the basis of Flash Dose (Fuisz Technologies, Chantilly, VA.). In this technology, saccharides or polysaccharides are processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The floss is then partially recrystallised to impart a good flow properties and compressibility. The floss then can be milled and blended with active ingredient/s and other excipients and finally compressed in to RDT.

Advantages of this technology are that tablet can accommodate high doses and possess satisfactory mechanical strength. The candyfloss are hygroscopic, hence, their manufacturing requires control of humidity conditions.
Table 1.3: Summary of advantages and disadvantages of different technologies for preparing rapid disintegrating dosage form

<table>
<thead>
<tr>
<th>Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeze-drying</td>
<td>Immediate dissolution (&lt; 5 sec)</td>
<td>Very poor physical resistance, High cost of production, Low dose of water soluble drugs</td>
</tr>
<tr>
<td>Moulding</td>
<td>Very rapid disintegration (5-15 sec), high dose</td>
<td>High cost of production, Weak mechanical strength, Possible limitation in stability.</td>
</tr>
<tr>
<td>Standard tableting</td>
<td>Low cost of production, High dose, Use of standard equipments, Good physical resistance.</td>
<td>Disintegration capacity markedly limited by, size and hardness of the tablet.</td>
</tr>
<tr>
<td>Effervescent tableting</td>
<td>Use of standard equipments, High dose, Good physical resistance, Pleasant effervescent mouthfeel.</td>
<td>Operating in controlled low humidity, need specialized packaging i.e. totally impermeable blister.</td>
</tr>
</tbody>
</table>
1.4.3 Patented Technologies For Fast Dissolving Tablets:

Some patented technologies are described here (Table No.3). Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies in the following respects:

- Mechanical strength of final product;
- Drug and dosage form stability;
- Mouthfeel
- Taste
- Rate of dissolution of drug formulation in saliva;
- Swallowability;
- Rate of absorption from the saliva solution;
- Overall bioavailability.

Table 1.4: Some Patented Technologies For Fast Dissolving Tablets

<table>
<thead>
<tr>
<th>Technology</th>
<th>Company’s name</th>
<th>Technology base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durasolv, Orasolv</td>
<td>CIMA Labs Inc.</td>
<td>Molding</td>
</tr>
<tr>
<td>Flash Tab</td>
<td>Ethypharm</td>
<td>Molding</td>
</tr>
<tr>
<td>Wow Tab</td>
<td>Yamanouchi Pharma</td>
<td>Molding</td>
</tr>
<tr>
<td>Flash dose</td>
<td>Fuisz Technology Ltd</td>
<td>Cotton candy process</td>
</tr>
<tr>
<td>Ziplets</td>
<td>Eurand</td>
<td>Molding</td>
</tr>
<tr>
<td>Fast Melt</td>
<td>Elan Corp.</td>
<td>Molding</td>
</tr>
</tbody>
</table>
1.5 DRUG PROFILE$^{112,113}$:

1.5.1 Nicorandil

A derivative of Niacinamide that is structurally combined with an organic nitrate. It is potassium channel opener that causes vasodilation of arterioles and large coronary arteries. Its nitrate like property produces venous vasodilation through stimulation of guanylate cyclase.

* **Structural Formula:**

```
\[ \begin{align*}
\text{\textbf{O}} & \text{\textbf{N}} \\
\text{\textbf{H}} & \text{\textbf{\text{-}}} \\
\text{\textbf{C}} & \text{\textbf{-}}} \\
\text{\textbf{H}} & \text{\textbf{-}}} \\
\end{align*} \]
```

* **Chemical Name:** N-[2-(nitroxy) ethyl]-3-pyridinecarboxamide.

* **Molecular Formula:** C$_8$H$_9$N$_3$O$_4$

* **Molecular Weight:** 211.18

* **Melting range$^{113}$:** 92-93 °C

* **Category:** Antianginal.

* **Dose:** Usual initial dose is 10 mg twice daily, increased as necessary to a maximum of 30 mg twice daily. The usual therapeutic dose is in the range of 10 to 20 mg twice daily.

* **Description:** White crystalline powder, odorless with bitter taste.

* **Solubility:** Soluble in water, ethanol, but insoluble in chloroform.

* **Storage:** Store in cool dry place, protected from light.
Mechanism of action:
Nicorandil activates ATP sensitive k⁺ channels leading to hyper polarization of vascular smooth muscles and decreasing vasoconstriction and consequent angina. Like nitrates, it acts as a NO donor and relaxes blood vessels by increasing cGMP. Thus arterial dilation is coupled with venodilation. Coronary flow is increased. No significant cardiac effects on contractility and conduction have been noted.

Pharmacokinetic properties:
Absorption: It is readily absorbed from gastrointestinal tract after oral administration.
Metabolism: The liver does not metabolize it significantly during passage through the portal system (lack of first pass effect). Thus, it easily enters the systemic blood flow, resulting in almost complete bioavailability (75-100%). Nicorandil is metabolized extensively by denitration.
Excretion: The major route of elimination is the kidney. Less than 2% of the dose is excreted through the biliary route. The parent drug is excreted poorly in urine. 2-nicotinamidoethanol, a pharmacologically inactive denitrated metabolite, is the major Nicorandil related compound excreted in urine.

C_max: 300 ng / ml
T_max: 30 min.
Plasma Half Life: approximately 1 hr.
Volume of distribution: approximately 1 lit / kg body weight.
Total body clearance: 1.15 L/min.
Protein binding: approximately 25 %.

Therapeutic uses:
Nicorandil is a vasodilator. It is potassium channel opener providing vasodilatation of arterioles and large coronary arteries. Its nitrate component produces venous vasodilation through stimulation of Guanylase cyclase.

Drug interactions:
Tricyclic antidepressants and alcohol may cause hypotension.
Chapter 1

Introduction

\* Adverse effects:

\* Headache
\* Cutaneous vasodilation
\* Nausea, vomiting
\* Dizziness, weakness
\* Mouth ulcer.

\* Contraindications:

\* Patients with cardiogenic shock
\* Left ventricular failure with low filling pressure
\* Hypoglycemia
\* Low blood pressure
\* Acute pulmonary oedema.

\* Overdosage:

Reduction in blood pressure and/or increase in heart rate may occur with high doses.

\* MARKETED PREPARATIONS\textsuperscript{14}:

\* DILNICON TAB 5 mg/10mg
\* KORANDIL TAB 5 mg/10mg
\* NIKORAN INJ 2mg/48 mg
\* ZYNICOR TAB 5mg
1.5.2 Metoclopramide Hydrochloride\textsuperscript{115,116}

*Structural Formula*

\hline
\text{Chemical Name:} 4-amino-5-chloro-N-(2-diethylaminoethyl) 2-methoxybenzamide hydrochloride. \\
* Molecular Formula: \text{C}_{14}\text{H}_{22}\text{ClN}_{3}\text{O}_{2} \cdot \text{HCl} \\
* Molecular Weight: 299.8 \\
* Category: Antiemetic. \\
* Dose: Oral Dose 5-10 mg thrice daily. \\
\hspace*{1cm} Parenteral Dose 10-20 mg IM or IV \\

*Description:* A white or almost white, odorless or almost Odorless, crystalline powder \\

*Solubility:* Very soluble in water; freely soluble in alcohol; Sparingly soluble in chloroform & in methylene Chloride; practically insoluble in ether. \\

*Melting point\textsuperscript{117}: 182-184°C \\

*Storage:* Store in airtight container, protect from light. \\

*PKa:* \( P_{1}^{K} = 9.71, P_{2}^{K} = 0.42 \) \\

*Standards:* Metoclopramide HCl contains NLT 98.0% & NMT 101.0% of \( \text{C}_{14}\text{H}_{22}\text{ClN}_{3}\text{O}_{2} \cdot \text{HCl} \), calculated on the anhydrous basis.
• **Mechanism of action:**
  Metoclopramide has central antiemetic action as it prevents vomiting induced by apomorphine. It probably acts by blocking the dopaminergic receptors in the CTZ.

• **Pharmacokinetic properties:**
  Metoclopramide hydrochloride is rapidly & almost completely absorbed from the gastro-intestinal tract following oral administration.
  \[ T_{\text{max}}: 2 \text{ hrs.} \]
  \[ C_{\text{max}}: 80\text{ng/ml.} \]
  \[ V_d: 3.4\pm1.3 \text{ liters/kg.} \]
  \[ \text{Half-life: 5.0\pm1.4hrs} \]

• **Therapeutic uses:**
  **As an Antiemetics**
  - To accelerate gastric emptying
  - To treat gastro paresis
  - To treat reflux esophagitis
  - Before and during cancer chemotherapy to prevent nausea & vomiting.

• **Contraindications:**
  - Patients with GI hemorrhage,
  - Obstruction or perforation
  - Hypersensitive
  - Seizure disorders.
  - Pheochromocytoma,
  - A hypertensive crisis.

• **Drug interactions:**
  Atropine (and related anticholinergic compounds) and narcotic analgesics may negate the GI motility effects of Metoclopramide. The GI stimulatory effects of Metoclopramide may affect the absorption of many drugs.
Drugs that dissolve, disintegrate and/or are absorbed in the stomach (e.g., digoxin) may be absorbed less. Due to its small particle size, Lanoxin® brand of digoxin is apparently unaffected by Metoclopramide administration. Metoclopramide may enhance absorption of drugs that are absorbed primarily in the small intestine (e.g., cimetidine, tetracycline, aspirin, & diazepam). Metoclopramide may accelerate food absorption and thereby alter insulin doses and/or timing of insulin effects. Phenothiazines (e.g., acepromazine, chlorpromazine, etc.) and butyrophonenes (e.g., droperidol, azaperone) may potentiate the extra pyramidal effects of Metoclopramide. Other sedatives, tranquilizers and narcotics may enhance the CNS effects of Metoclopramide.

? Unwanted Effects:
- Drowsiness, dystonic or EP reactions.
- Others include diarrhoea, lassitude, Skin rash, gynecomastia
- Galactorrhoea.

? Marketed preparations
- EMENIL TAB 10 mg
- MAXERON TAB 10mg, SYR 5mg/ml
- REGLAN TAB 10mg, SYR 5mg/ml
- MAXINORM TAB 10mg
- PERINORM DT-TAB 5mg, SYR 5mg/ml
- Metoclopramide HCl Injection 5 mg/ml in 2 & 10 ml amps, and 2, 10, 30,50 & 100 ml vials (some contain preservatives, some are preservative free and labeled for single-use only); Reglan® ; Metoclopramide HCl® (Quad)
1.5.3 Ondansetron Hydrochloride

* Chemical Name: (±)-2,3-Dihydro-9-methyl-3- (2-methylimidazol-1-yl) methyl carbazol-4 (1H)-one monohydrochloride dihydrate.

* Molecular Formula: C18H19N3O.HCI

* Molecular Weight: 390.87

* Melting point: 178-180°C

* Category:
  - Anti-anxiety Agents
  - Antipsychotics
  - Antipruritics
  - Antiemetics
  - Serotonin Antagonists

* Dose: 8 mg as a slow I.V. injection given just before chemotherapy, radiotherapy, or 8 mg orally 1-2 hours before. This is followed by 8 mg orally every 12 hours.

* Description: White to off white powder

* Solubility: Sparingly soluble in water & in alcohol; soluble in methanol; slightly soluble in Isopropyl alcohol & in dichloromethane, very slightly soluble in acetone; in chloroform & in ethyl acetate.

* Storage: Preserve in tight, light resistant container.

* Mechanism of action:

Ondansetron is a selective serotonin 5-HT3 receptor antagonist. The serotonin 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin
from the enterochromaffin cells of the small intestine, and that the released serotonin then activates 5-HT₃ receptors located on vagal efferents to initiate the vomiting reflex. Therefore Ondansetron works by blocking the reception of serotonin at these 5-HT₃ receptors.

* **Pharmacokinetic properties:**

  After oral administration Ondansetron is completely absorbed from GI tract.

  * $V_d$: 1.9±0.05 liters/kg
  * **Half-life**: 3.5±1.2 hrs
  * $T_{max}$: 1 hrs
  * $C_{max}$: 39ng/ml.

  * **Protein binding:** 70%-76% (Plasma protein binding)

* **Therapeutic uses:**

  Ondansetron hydrochloride is indicated for vomiting and nausea associated with cytotoxic radiotherapy & chemotherapy, prophylaxis & treatment of postoperative vomiting and nausea.

* **Contraindications:** Hypersensitivity

* **Drug interactions:** Dexamethasone enhances the effect of the drug.

* **Marketed preparations**
  - ZOFRAN® (ondansetron hydrochloride) Tablets
  - ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets
  - ZOFRAN® (ondansetron hydrochloride) Oral Solution
1.5.4 Cephalexin Monohydrate 122,123

* **Structural Formula:**

![Structural Formula](image)

* **Chemical Name:** 7- Q - D- phenylglycylamine -3- methyl- 3- cephem-4.carboxylic acid monohydrate.

* **Molecular Formula:** C_{16}H_{17}N_{3}O_{4}S, H_{2}O

* **Molecular Weight:** 365.40

* **Melting range:** 326.8 °C

* **Category:** Antibiotic.

* **Dose:** 1 to 4 gm daily in divided doses.

* **Description:** White or almost white, crystalline powder with characteristic odor and bitter taste.

* **Solubility:** Slightly soluble in water, practically insoluble in ethanol (95 %), in chloroform and in ether.

* **Storage:** Store in well-closed, light-resistant containers in cool place.

* **pKa:** 4.5

* **Standards:** Cephalexin contains not less than 95.0% and not more than 101.0% of C_{16}H_{17}N_{3}O_{4}S, calculated with reference to anhydrous substance.

* **Mechanism of action:** By binding to the specific penicillin-binding proteins located inside the bacterial cell wall, Cephalexin inhibits the last stage of bacterial cell wall synthesis.

* **Pharmacokinetic properties:**

  * **Absorption:** It is almost completely absorbed from gastrointestinal tract after oral administration.

  * **Metabolism:** Cephalexin is not metabolized.
Excretion: 90% of the drug is excreted unchanged in the urine.

Cmax: 18 mcg/ml

Plasma Half Life: about 1 hr.

Volume of distribution: about

Protein binding: 14%.

Therapeutic uses:

Cephalexin is indicated for the treatment of:
- Respiratory tract infections
- Skin and skin structure infections
- Genitourinary tract infections

Side effects:

- Abuse potential
- Allergic reaction (difficulty in breathing, closing of throat)
- Rash, redness or itching
- Severe nausea, vomiting or diarrhoea
- Mucous or blood in stool.

Overdose:

- Nausea, vomiting
- Diarrhea,
- Abdominal cramps,
- Seizures,
- Numbness,
- Muscle spasms

Marketed Preparations:

- CEFAX capsules 250 mg / 500mg
- CEPHADEX DT 250 mg / 125 mg
- CEFF dry syrup 125 mg / 5 ml
1.6 RESIN PROFILES

Profiles of available cation exchange resins for taste abatement of bitter drugs are given in Table 1.5 to 1.8

1.6.1 Strong Resins

Table 1.5: Profiles of Tulsion – 343, Tulsion – 344, Indion – 224

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tulsion-343</th>
<th>Tulsion-344</th>
<th>Indion-224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Strong acid cation exchange resin</td>
<td>Strong acid cation exchange resin</td>
<td>Strong acid cation exchange resin</td>
</tr>
<tr>
<td>Matrix structure</td>
<td>Polystyrene copolymer</td>
<td>Polystyrene copolymer</td>
<td>Polystyrene copolymer</td>
</tr>
<tr>
<td>Functional group</td>
<td>Sulphonic</td>
<td>Sulphonic</td>
<td>Sulphonic</td>
</tr>
<tr>
<td>Ionic form</td>
<td>H⁺</td>
<td>Na⁺</td>
<td>H⁺</td>
</tr>
<tr>
<td>Particle size (mm)</td>
<td>&lt;0.15</td>
<td>&lt; 0.15</td>
<td>0.2-1.2</td>
</tr>
<tr>
<td>Total exchange capacity</td>
<td>4.5 meq/ml</td>
<td>4 meq/ml</td>
<td>4.8 meq/gm</td>
</tr>
</tbody>
</table>

1.6.2 Weak Resin

Table 1.6: Profiles of Indion – 214, Amberlite IRP 64, Tulsion – 335

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Indion-214</th>
<th>Amberlite IRP 64</th>
<th>Tulsion - 335</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Weak acid cation exchange resin</td>
<td>Weak acid cation exchange resin</td>
<td>Weak acid cation exchange resin</td>
</tr>
<tr>
<td>Matrix structure</td>
<td>Polymethyl acrylate copolymer</td>
<td>Methacrylic acid copolymer</td>
<td>Methacrylic acid Copolymer</td>
</tr>
<tr>
<td>Functional group</td>
<td>-COOH⁺</td>
<td>-COOH⁺</td>
<td>-COOH⁺</td>
</tr>
<tr>
<td>Ionic form</td>
<td>H⁺</td>
<td>H⁺</td>
<td>H⁺</td>
</tr>
<tr>
<td>Particle size (mm)</td>
<td>&lt;0.15</td>
<td>&lt; 0.15</td>
<td>&lt; 0.15</td>
</tr>
<tr>
<td>Total exchange capacity</td>
<td>10.0 meq/gm</td>
<td>10 meq/ml</td>
<td>10 meq/gm</td>
</tr>
</tbody>
</table>
**Table 1.7: Profiles of Indion – 204 and Micpol 1061**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ion Exchange Resin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indion-204</td>
</tr>
<tr>
<td>Type</td>
<td>Weak acid cation exchange resin</td>
</tr>
<tr>
<td>Matrix structure</td>
<td>Polyacrylic copolymer</td>
</tr>
<tr>
<td>Functional group</td>
<td>-COOH^+</td>
</tr>
<tr>
<td>Ionic form</td>
<td>H^+</td>
</tr>
<tr>
<td>Particle size (mm)</td>
<td>&lt;0.15</td>
</tr>
<tr>
<td>Total exchange capacity</td>
<td>10.0 meq/gm</td>
</tr>
</tbody>
</table>

**Table 1.8: Profiles of Tulsion – 339, Indion – 294 and Amberlite IRP 88**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ion exchange resins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tulsion – 339</td>
</tr>
<tr>
<td>Type</td>
<td>Weak acid cation exchange resin</td>
</tr>
<tr>
<td>Matrix structure</td>
<td>Methacrylic acid Copolymer</td>
</tr>
<tr>
<td>Functional group</td>
<td>-COO^- K^+</td>
</tr>
<tr>
<td>Ionic form</td>
<td>K^+</td>
</tr>
<tr>
<td>Particle size (mm)</td>
<td>&lt; 0.15</td>
</tr>
<tr>
<td>Total exchange capacity</td>
<td>10 meq/gm</td>
</tr>
</tbody>
</table>

****

Taste Abatement of Bitter Drugs using Ion Exchange Resins and Development of their Oral Formulations.