# CHAPTER II

# LITERATURE REVIEW

## 1. Ion exchange resin properties

Ion exchange resins consist of spherical beads approximate 0.5-1.2 mm in diameter and swell in water to 2-3 times from their original weight (Figure 1). The insolubility of ion exchange resins depends on the nature of the counter ion and the extent of crosslinking of the basic skeleton (Anand et al., 2001). Ion exchange resins contain positive and negative charge sites. They are thus classified as either cationic or anionic exchangers (Swarbrick and Boylan, 1988). Within each category, they are classified as strong or weak, depending on their affinity for soluble counter ions. The strong cation exchange resins contain sulfonic acid sites whereas weak cation exchange resins are based on carboxylic acid moieties. The strong anion exchange resins have quaternary amine ionic sites, whereas weak anion exchange resins have predominantly tertiary amine substituents.

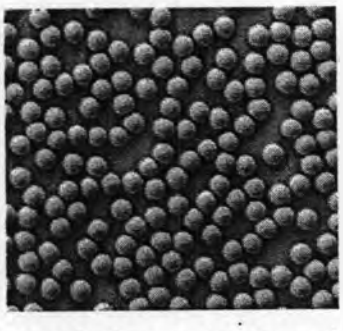


**Figure 1** Ion exchange resins.

### 1.1 Polymer matrix

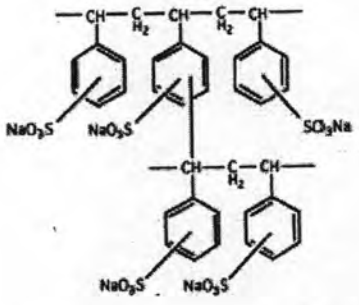
In chemical, ion exchange resins are made up of a structural component consisting of the polymer matrix and a functional component to which the counter ion is bound. The most common used polymer backbone for anion exchange and strong cation exchange resins are based on polystyrene (Figure 2). Divinylbenzene (DVB) is included in the copolymerization for crosslinking the polymer chains. The amount of

divinylbenzene, usually expressed as percentage by weight, has a strong effect on the physical properties. The weak cation exchange resins are generally polyacrylic or polymethacrylic acids, also with divinylbenzene as the crosslinking agent (Swarbrick and Boylan, 1988). Table 1 describes the most common ion exchange resins in use.

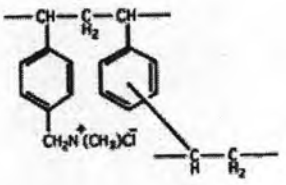
**Table 1** Common ion-exchange resins

| Type | Exchange species | Polymer Backbone | Commercial Resins | pKa |
|---|---|---|---|---|
| Strong cation | $-SO_3H$ | Polystyrene-DVB | Amberlite®IR120, DOWEX®50 | < 1 |
| Weak cation | COOH | Methacrylic acid-DVB | Amberlite®IRC50 | 4-6 |
| Strong anion | $N^+(CH_3)_3$ | Polystyrene-DVB | Amberlite®IR400, DOWEX®1 | > 13 |
| Weak anion | $N^+(CH_3)_2$ | Polystyrene-DVB | Amberlite®IR4B, DOWEX®2 | 7-9 |

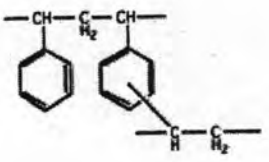
Weak cation exchange resins have a pKa value of about 4-6, so at pH 4 or above their exchange capacity tends to increase. Strong cation exchange resins which have a pKa value of about 1 are highly dissociated at all pH range in the gastrointestinal tract. Carboxylic acid resins that have a pKa of 5.2 or higher tend to have too rapid release in simulated gastric fluid to be use as a sustained release product. Resin that have a pKa less than 5.2 give sustained release of the drug during dissolution studies in simulated gastric fluid followed by simulated intestinal fluid.



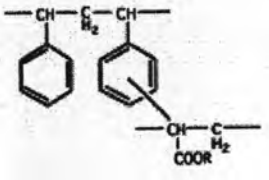
**Sodium Polystyrene Sulfonate**



**Cholestyramine**



**Styrene-divinylbenzene Copolymer**



**Polyacrylester**

**Figure 2** Structure of resins (Takenaga et al.,1998).

## 1.2 Exchange process and equilibrium

The principal characteristic of resins is their capacity to exchange in solution. Soluble ions are removed from solution through exchange with the counterions absorbed on the resin as illustrated in equations (1), (2),(3) and (4) (Swarbrick and Boylan, 1988).

For strong and weak cation exchange resins :

$$Re\text{-}SO_3^- H^+ + drug^+ \rightleftharpoons Re\text{-}SO_3^- drug^+ + H^+ \quad (1)$$

$$Re\text{-}COO^- H^+ + drug^+ \rightleftharpoons Re\text{-}COO^- drug^+ + H^+ \quad (2)$$

For strong and weak anion exchange resins :

$$Re\text{-}N(CH_3)_3^+ Cl^- + drug^- \rightleftharpoons Re\text{-}N(CH_3)_3^+ drug^- + Cl^- \quad (3)$$

$$Re\text{-}NR_1R_2^+ Cl^- + drug^- \rightleftharpoons Re\text{-}NR_1R_2^+ drug^- + Cl^- \quad (4)$$

These exchangers are equilibrium reaction. The extent of exchange is governed by the relative affinity of the resin for particular ions. Relative affinity between ions may be expressed as a selectivity coefficient derived from the mass-action expression given in equation (5).

$$K = \frac{[D]_r[M]_s}{[D]_s[M]_r} \quad (5)$$

Where K is the rate of reaction, $[D]_r$ is the drug concentration in resin and $[D]_s$ its concentration in the solution, and $[M]_r$ is the counterion concentration in the resin, and $[M]_s$ its concentration in the solution.

Factors that influence on selectivity including valence, hydrated size, pKa and the pH of the solution. When loading the resin with an ion of less affinity, the exchange may be driven toward the direction of unfavorable equilibrium by flooding the fluent with high concentrations or by using chromatographic column procedures.

### 1.3 Exchange capacity

The exchange capacity refers to the number of ionic sites per unit weight or volume (meq per gram or meq per ml). The 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 (Swarbrick and Boylan, 1988). Carboxylic acid resins which derived from acrylic acid polymers have higher exchange capacities (about 10 meq/gm) than sulfonic acid (about 4 meq/gm) or amine resins because of bulkier ionic substituents. Therefore, higher drug percentages may often be achieved with carboxylic acid resins.

### 1.4 Degree of crosslinkage

The degree of crosslinkage is controlled by the percent divinylbenzene used in the copolymerization. In commercial resins, this is generally designated by X followed by the percentage divinylbenzene. The degree of crosslinkage usually varies between 2 to 12 % of the copolymer (Swarbrick and Boylan, 1988). Increasing in crosslinkage of the polymer network will decrease both drug binding and its subsequent release (Irwin et al., 1987). This parameter influences the porosity and swelling properties of resin. Low crosslinkage agent swells markedly upon hydration while the higher grades have a tighter pore structure. Shrinkage of the resin when the cationic form is brought into contact with acid solutions may also occur. This may cause a reduction in pore diameter and lead to the entrapment of large molecule ions (Irwin et al., 1987). Even after absorption, some large molecules may be difficult to elute unless the divinylbenzene percentage is low. The swelling capacity of the wet ion exchange resins has been put to practical use with the potassium form of the polymethacrylic acid resin, Amberlite®IRP-88, as a tablet disintegrating agent.

### 1.5 Particle size

Ion exchange resins are commercially available in different size ranges, generally expressed in micrometer or mesh ranges. The most common used are spherical beads of 297-840 microns (20-50 mesh). Particle size had a little effect on

the ultimate amount of drug bound by the resin but tend to effect drug release inversely. The particle size of resins is important factors in determining release from resinate. The rate of ion exchange interactions are increased as the resin diameter decreases due to a reduction in the diffusive path length (Irwin et al., 1987).

## 2. Selection of ion exchange resins

The selection of ion exchange resin for drug delivery applications is primarily governed by the functional group properties of the ion exchange resin (cation or anion exchanger). However, the following factors need to be considered during selection such as capacity of ion exchange resin, degree of crosslinkage in the resin matrix, particle size, nature of drug and site of drug delivery. It is also important to evaluate the resin in the pH and ionic strength environment.

For rapid dissolution in the GI tract, weak cation or anion exchange resins, low crosslinkage and small particle size are required. Slow release or maximum taste protection may be obtained with strong cation or anion exchange resins, high crosslinkage and large particle size. Maximum drug loading required low molecular weight drug and low crosslinkage resins. A high molecular weight often limits the drug ability to be absorbed and very low crosslinkage may be necessary for meaningful loadings (Anand et al., 2001).

## 3. Gastrointestinal release mechanism

Bioavailability of drug absorbed on ion exchange resins depends on both transit of the particles through the GI tract and drug release kinetics. Drug release or dissolution from the resin can occur only by replacement of the drug by another ion with the same charge (Figure 3). Since the exchange is an equilibrium process, it depends on the ionic constitution of body fluid and the fluid volume (Swarbrick and Boylan, 1988).

If the drug-resin complex is administered orally, a small amount of drug may be released. This would be followed by significant and continuous release in the stomach where the drug is exposed to high acid and chloride concentrations. Anionic exchange

resins and the strong cation exchangers release a limited amount of drug in the stomach as shown in equation (6) and (7). In contrast, drug bound to weakly acidic carboxylic acid is released much more readily in the stomach as illustrated in equation (8). The high pKa of the resin drives the equilibrium toward the formation of undissociated acid in a low pH environment. This may promote rapid drug release.

In the stomach :

$$Re\text{-}SO_3^- drug^+ + H^+ \rightleftharpoons Re\text{-}SO_3^- H^+ + drug^+ \quad (6)$$

$$Re\text{-}N(CH_3)_3^+ drug^- + Cl^- \rightleftharpoons Re\text{-}N(CH_3)_3^+ Cl^- + drug^- \quad (7)$$

$$Re\text{-}COO^- drug^+ + H^+ \rightleftharpoons Re\text{-}COO^- H^+ + drug^+ \quad (8)$$

In the intestine, the neutral pH will keep all ionic sites on the resins ionized and the exchange process will occur continuously. The absorption of solubilized drug will drive the equilibrium further toward drug release. In the large intestine, desorption from the resin and absorption may be slow considerably due to low fluid content, entrapment in fecal matter and poor membrane absorption.

In the intestine :

$$Re\text{-}SO_3^- drug^+ + Na^+ \rightleftharpoons Re\text{-}SO_3^- Na^+ + drug^+ \quad (9)$$

$$Re\text{-}N(CH_3)_3^+ drug^- + Cl^- \rightleftharpoons Re\text{-}N(CH_3)_3^+ Cl^- + drug^- \quad (10)$$

The highly insoluble resin is not absorbed. It is simply eliminated from the body with the counterions that have replaced the drug. In theory, complete dissolution of drug from the ion exchange resin during GI transit is impossible because of the equilibrium mechanism of release. However, in practice, complete bioavailability frequently occurs.

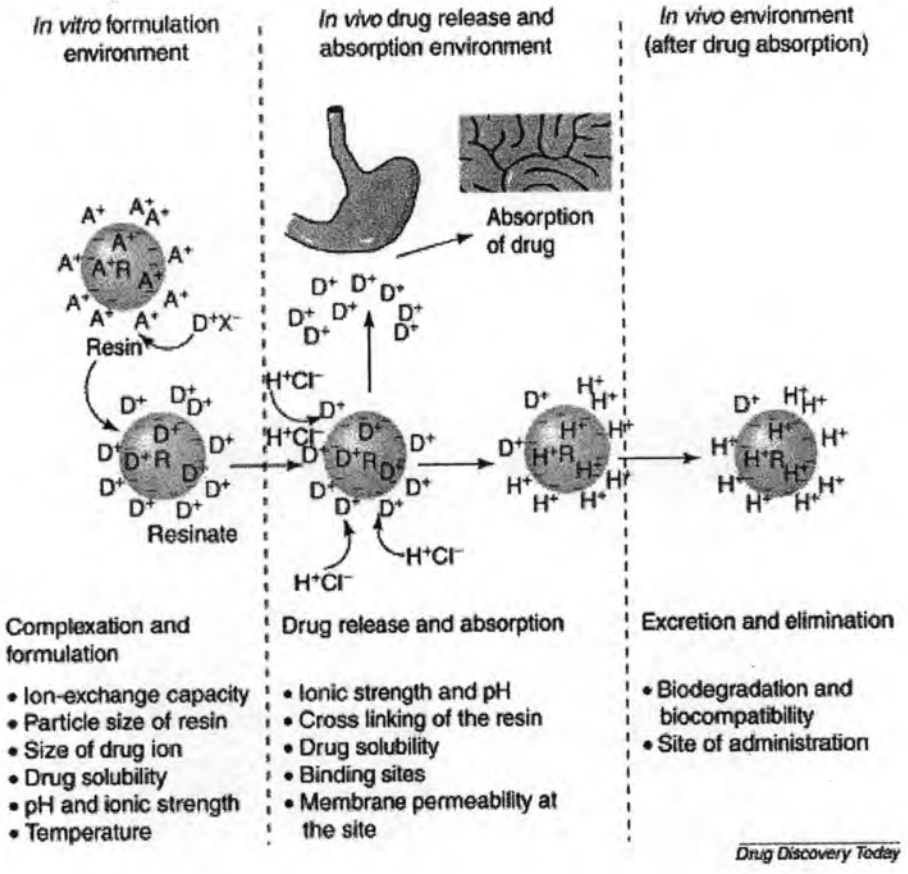



**Figure 3** Gastrointestinal sustained release mechanism (Anand et al., 2001).

## 4. Preparation and evaluation of resinates

Purification of resin by washing with ethanol and deionized water to removes the impurities. If it does not have the desired counter ions, changing the ionic form of ion exchange resin might occasionally be required to convert a resin form to another. Strong acidic cation exchange resins are usually marketed in $Na^+$ form and strongly basic anion exchange resins in $Cl^-$ form. They are generally converted into hydrogen and hydroxide forms. The conversion can be achieved by soaking the resins with acid or alkali solutions. After changing the ionic form, the resins are subjected to wash with deionized water until the elute becomes neutral in reaction and dried at 50°C.

Resinate preparation is normally done by batch technique or column technique. Since the reaction is an equilibrium phenomenon, maximum potency and efficiency are best obtained by the column technique. However, the batch technique is much simpler and quicker (Anand et al., 2001).

### 4.1 Batch technique

After suitable pretreatment, a specific quality of the resin is agitated with the drug solution until the equilibrium is obtained.

### 4.2 Column technique

Resinate is formed by passing a concentrated solution of drug through the ion exchange packed column until the effluent concentration is the same as the eluent concentration.

Since the ion exchange resins are insoluble in all common solvent, determination of the drug content requires complete elution from the resin. This is usually best accomplished in an aqueous medium although it is difficult when the affinity of the drug to the resin is strong. The high selectivity coefficients associated with many drugs often require a large excess of competing counterion to approach complete displacement. The best method to ensure quantitative drug recovery is by sequential slurries with high concentrations of counterions.

## 5. Microencapsulation and particle coating

Drug from the resinates will be slowly released when compared to the drug particles but will also be significantly faster than the modified resinates, coated or microencapsulated. Without coating, the ion exchange process begins within seconds and drive toward equilibrium very quickly. Applying a polymer coating to the ion exchange resin complex can delay and slow down the elution process. Taste coverage may be improved with a coating that delays drug dissolution in the mouth for several minutes. Controlled release system can be finely controlled with barrier or semipermeable membranes. Acid labile drugs may be protected from stomach acid by microencapsulation with an acid-insoluble enteric coating. The release of diclofenac at the desired rate to avoid gastric irritation was achieved for arthritic patients (Swarbrick and Boylan, 1988).

The polymer beads may be coated by coacervation or physical procedures. Air suspension coating systems appear to be the most useful and versatile (Ichikawa et al., 2001). The ion exchange resin particles offer a receptive substrate for this method, being compact highly insoluble polymers with fairly narrow particle size ranges. Coating may be further stabilized by impregnating with polyethylene glycol as protection against resin swelling.

Several researches have succeeded in using microencapsulated or coated resinates and most of patented and marketed formulations belong to this category. Microencapsulation of resinates provides better control over the drug release because of the presence of a rate controlling membrane. The absorption of the drug from coated resinates is a consequence of the entry of the counter ions into the coated resinate, release of drug ions from the drug resin complex by the ion exchange process and diffusion of drug ions through the membrane into the surrounding absorption environment. Often, water-insoluble coating materials are used, such as ethylcellulose (Motycka et al., 1985; Chow et al., 1990; Wen et al., 1999), acrylate polymer (Ichikawa et al., 2001) and polyethylene glycol (Pisal et al., 2004). The release rate at the desired level can be turned by optimization of coating thickness. Microencapsulation of resinates can be achieved by air suspension coating (Wurster process) (Ichikawa et al., 2001), interfacial polymerization, solvent evaporation (Halder and Sa, 2006) or pan coating method.

Further modification of the resinate coating for improving the drug release pattern has been the concept of Pennkinetic systems (Fisons BV, Rochester, NY, USA, originally patented by Pennwalt Corporation). In this system, resinates are pretreated with polyethylene glycol 400 to maintain the geometry and improve the coating process. The pretreated resinates are coated with ethyl cellulose or any other water-insoluble polymer. Polyethylene glycol helps in controlling the swelling rate of the resinate matrix in water while an outer ethyl cellulose coating modifies the diffusion pattern of ions both in and out of the system. Two over-the-counter (OTC) products, dextromethorphan cough syrup (Delsym®, Fisons) and codeine and chlorpheniramine syrup (Phentuss®, Fisons), are the examples of marketed formulations of Pennkinetic systems.

## 6. Applications of ion exchange resins in drug delivery

### 6.1 Sustained release systems

A major problem of controlled or sustained release system is dose dumping that resulting in increased risk of toxicity. The use of ion exchange resin has occupied an important place in the development of sustained release because of their better drug retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (chemical) properties of ion exchange resin will release the drug more uniformity than that of simple matrix which have only physical properties. Moreover ion exchange resins have flexibility in designing a variety of delivery systems such as liquid, beads, microparticles and simple matrix.

Resinates alone are the simplest forms of controlled or sustained release delivery systems. Resinates can be filled directly in capsule, suspended in liquids, suspended in matrix or compressed into tablets.

#### 6.1.1 Sustained release liquids

The best application of ion exchange resins as drug carriers is their use in sustained or controlled release liquids. Although alternative methods are available in preparing sustained release solid products, the resin technique offers one of very few usable systems for achieving ready made liquid products with prolonged release. In liquid form, the ion exchange resins can bind the drug in a liquid suspension by keeping the liquid free of counterions. When ingested, the ions in the body initiate gradual release from the resin. Although the properties of the drug-resin complex do not give the desired sustained release rate, coating the particles with a rate controlling membrane often achieves the target bioavailability. The Pennkinetic system, developed by the Pennwalt Corporation, is the most notable application of this technique (Swarbrick and Boylan, 1988).

Delsym® is a liquid suspension product designed to provide 12 hours relief of coughs caused by minor throat and bronchial irritation. The active agent is dextromethorphan which is bound to a sulfonic acid ion exchange resin and coated

with ethylcellulose. In a comparative bioavailability study, a single dose of this product was demonstrated to give blood levels of dextromethorphan comparable to two units of 6 hours dose of dextromethorphan hydrobromide solution over a 12 hours period.

Penntuss® is a combination product derived from the Pennkinetic system intended for 12 hours cough and cold relief. Both drugs are in the form of resinates bound to a sulfonic acid cation exchange resin. The codeine resinate particles are coated with ethylcellulose whereas the chlorpheniramine resinate particles are uncoated. Apparently, the chlorpheniramine has much greater affinity for the resin, and the equilibrium driven elution rate is sufficiently low to provide adequate prolonged release. Conversely, the codeine resin bonding is much weaker, and a rate controlling membrane must be added.

Liquifer® is a controlled release suspension containing iron in the ferrous state bound to a sulfonic acid ion exchange resin. It is designed to provide supplemental iron as a once a day dosage whereas constant blood levels are desired. The main purpose for controlled release of iron is to prevent high iron concentrations in the stomach which might cause gastrointestinal distress. In vitro equilibration studies indicated that no more than 25 % of the iron would be solubilized in the stomach. In addition to reduce gastrointestinal irritation, the resinate form of iron allows improved palatability and reduces tooth staining and the risk of toxic overdoses as compared to conventional liquid products.

Theophylline is widely used in asthma drug employed clinically in controlled release solid dosage formulations and desire to prepare a controlled release liquid product for pediatric. The ion exchange method appears variable, although the extremely weak acidity of theophylline (pKa = 8.77) makes the task much more difficult. Although the drug may be absorbed on the resin, the binding is too weak to allow equilibrium-driven controlled release. This must be achieved by barrier coatings. Motycka et al. (1985) first reported on a theophylline resinate system for controlled release using anion exchange resins. In vitro release rates were controlled with ethylcellulose and hard paraffin.

### 6.1.2 Sustained release capsules

A capsule dosage form containing spherical beads is an attractive drug delivery system because the beads have the following advantages such as high drug loading capacity, an ideal shape for coating or for controlled release of the active drug, good flow and a high surface area to volume ratio as compared to tablets (Schwartz et al., 1994). Absorbing an ionic drug on ion exchange resin and administering in a capsule or tablet dosage is an alternative for controlled release dosage. Biphetamine, capsule containing equal quantities of amphetamine and dextroamphetamine complexed to a sulfonic acid cation exchange resin, has been used for an antiobesity agent and for children behavior control. The recommended dosing is one or two times per day.

### 6.1.3 Sustained release tablets

The compaction of microcapsules or coated beads is usually offered in the pharmaceutical industry especially beads with a functional or rate controlling membrane. The basic problem is that without sufficient plasticity of the film, the coating could be destroyed under pressure and the rate control would be lost (Schwartz et al., 1994). Oral controlled released drug delivery systems based on matrix type tablets are generally prepared by blending a drug and carrier materials followed by compression (Sriwongjanya and Bodmeier, 1998). Drug release after compression of microcapsules may be faster or slower depending on the effect of compression on tablet porosity and microcapsule integrity (Prapaitrakul and Whitworth, 1990).

Phenylpropanolamine-resin complexes were microcapsulated with cellulose acetate butyrate using emulsion-solvent evaporation technique. Microcapsules were compressed with various diluents such as Emdex®, Fast Flo Lactose® and Avicel®. Microcapsule compressed with Avicel® had an acceptable physical properties and the least deterioration in the release profile (Prapaitrakul and Whitworth, 1989, 1990).

Propanolol hydrochloride and diclofenac sodium-resin complexes were incorporated into hydroxypropyl methylcellulose (HPMC) matrix tablets to modify the release of opposite charge drug. The release from drug-resin complexes tablets was significantly slower than from HPMC tablets containing drug without resin (Sriwongjanya and Bodmeier, 1998).

Dextromethorphan resinates were formed by a complexation with strong cation exchange resins, Dowex®50W (4 % crosslinkage 100-200 mesh) and Amberlite®IRP69 (8 % crosslinkage 100-140 mesh), to investigate the effect of different polysulfonate resins and direct compression fillers on physical properties. The plastic deformation of the fillers such as microcrystalline cellulose and spray dried rice starch caused a little change in the release of dextromethorphan (Pongjanyakul et al., 2005). Internal structure of DMP-resinate tablets prepared using microcrystalline cellulose at 4 MPa compression pressure was shown in Figure 4.

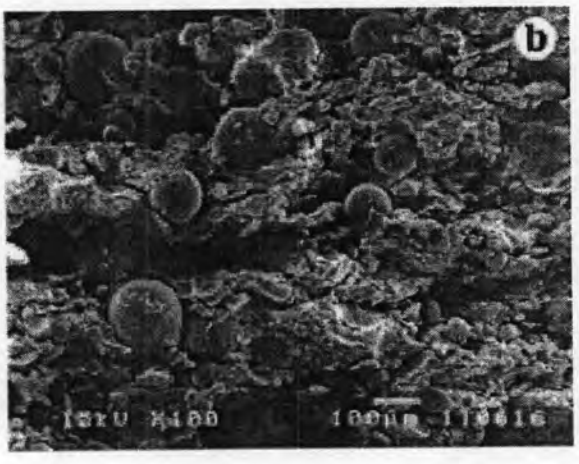



**Figure 4** Internal structure of DMP-resinate tablets prepared using MCC at 4 MPa compression pressure (Pongjanyakul et al., 2005).

### 6.1.4 Sustained release of dual-drug resinates

The formulation of dual ambroxal and chlorpheniramine resinates was prepared by the batch method. The drug release pattern from the resinate followed the

particle diffusion process. The amount of drug released from the dual ambroxal and chlorpheniramine resinate was not significantly different from that the classical ambroxal resinate and chlorpheniramine resinate (Akkaramongkolporn and Ngawhirunpat, 2003).

The dual-drug resinates which contain equivalent content of dextromethorphan hydrobromide (DTM) and diphenhydramine hydrochloride (DPH) was developed by using Dowex®50W resins. The release of DPH was mostly in faster rate and greater extent than that of DTM which might be explained by attribution of the hydrophobicity and the molecular size of the loaded drugs. The drug release from the resinates of resin 2 % crosslinkage and 4 % crosslinkage was found to be increasing with an increase in the ionic strength of release media. The increased ionic strength from 0.05 to 0.2 N KCl generally accelerated the release of both drug except for 0.4 N KCl solution in which the drug release from the resinates of high crosslinkage (8 % crosslinkage) was decrease. The congestion on the outward movement of drugs through the high crosslink matrix might cause the delay of drug release (Akkaramongkolporn et al., 2006). Table 2 give a comprehensive account of literature reports of various drug delivery systems using ion exchange resins.

**Table 2** Drug delivery systems using ion exchange resins

| Type of system | Drug | Ion exchange resin | Remarks |
|---|---|---|---|
| Resinates | Propanolol hydrochloride | Amberlite® and Dowex® | Irwin and Belaid (1987) |
| | Codeine | Resicat®ABM Na-042 | Plaizier-Vercammen (1992) |
| Dual-drug resinates | Dextromethorphan and Diphenhydramine | Dowex®50W | Akkaramongkolporn et al. (2006) |
| Pennkinetic | Phenylpropanolamine | Amberlite®IR-120 and Amberlite®XE-69 | Raghunathan et al. (1981) |
| Microencapsulated resinates | Theophylline | Dowex®1-x2, 1-x4, 1-x8 | Motycka et al. (1985) |
| | Phenylpropanolamine | Amberlite®IRP69 | Sprockel and Prapaitrakul (1988) |
| | Chlorpheniramine maleate, Propanolol HCl and Pseudoephedrne HCl | Amberlite®IRP69 | Sriwongjanya and Bodmeier (1997) |
| | Terbutaline | Dowex®50W-X4 | Cuna et al. (2000) |
| | Diclofenac sodium | Dowex®1-x2 | Ichikawa et al. (2001) |
| | Diltiazem hydrochloride | Indion® 254 | Halder and Sa (2006) |
| Compression of resinates | Phenylpropanolamine | - | Prapaitrakul and Whitworth (1989, 1990) |
| | Propanolol HCl | Amberlite®IRP69 | Sriwongjanya and Bodmeier (1998) |
| | Diclofenac sodium | Duolite®ATP-143 | Sriwongjanya and Bodmeier (1998) |
| | Dextromethorphan | Amberlite®IRP69 and Dowex®50W | Pongjanyakul et al. (2005) |

### 6.2 Site specific drug delivery systems

Delivering drug at the desired biological location could has several advantages in therapeutics such as

- Localizing the required drug concentration throughout the treatment.
- Reducing the systemic toxicity especially with cytotoxic anticancer drug.

- Preventing the drug degradation from the hostile environment.

Several studies reported the use of ion exchange resins for drug delivery at the desired site of action.

Prolong gastric retention of the drug formulations could improve the bioavailability and reduce drug wastage, especially for those predominantly absorbed from stomach. Examples of such drugs were frusemide, cyclosporin, allopurinol and ciprofloxacin. Floating dosage forms are one of the alternatives designed to prolong gastric residence of drugs. A novel floating extended release systems consisting of bicarbonate-charged resins coated with a semipermeable membrane was studied for improving gastric residence time (Atyabi et al., 1996). Drugs can simultaneously be complexed with the resins. The system floats in the stomach because of the exchange of chloride ions for bicarbonate counterparts, releasing the carbon dioxide. The release gas is trapped inside the membrane that causes the system to float. The preparation and mechanism of floating beads with a core of ion exchange resin was illustrated in Figure 5. Similar observation of floating controlled release was made with theophylline as a model drug (Atyabi et al., 1996).

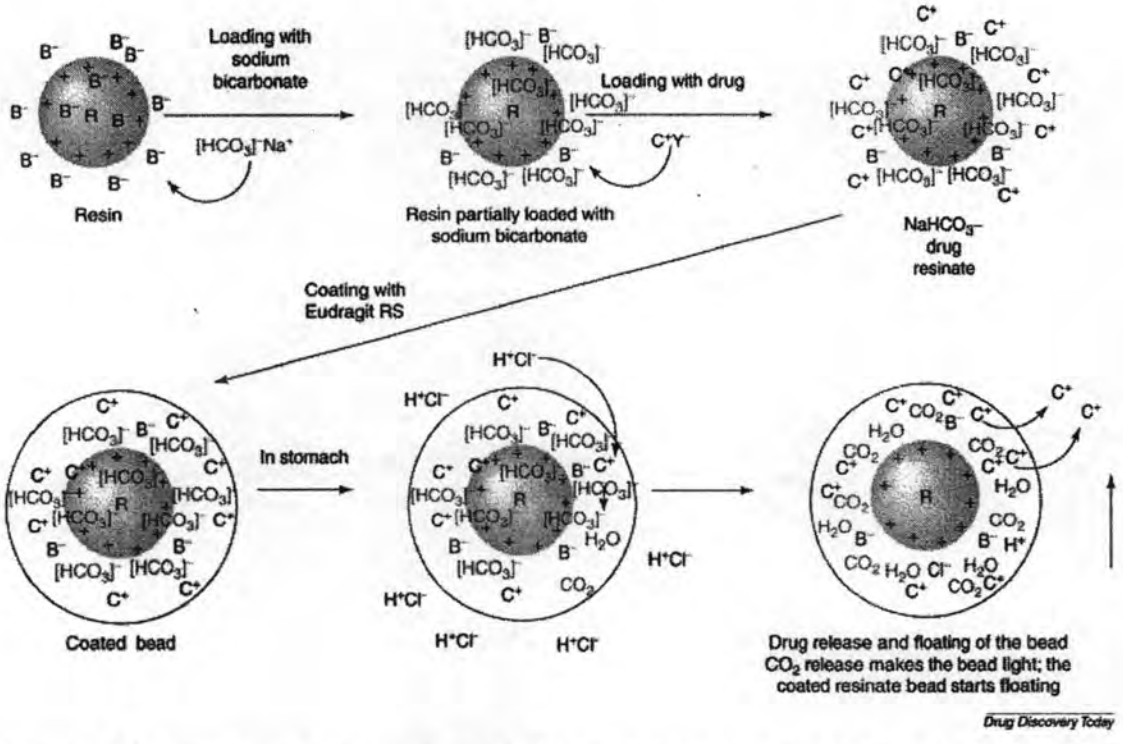



**Figure 5** Ion exchange mechanism of floating dosage forms (Anand et al., 2001).

Some ion exchange resins especially anion exchange resin such as cholestyramine possess bio/mucoadhesive properties which might be caused by their electrostatic interaction with the mucin and epithelial cell surface. The use of such bioadhesive ion exchange resin is another attractive approach in the development of targeted formulations for the GIT. This approach would enhance to the site of *Helicobacter pylori* colonization (fundus) which conventional dosage forms fail to reach. Similar types of applications were found which bioadhesive ion exchange resin. These systems are also useful in the delivery of diagnostics.

### 6.3 Taste masked oral drug delivery systems

The taste of pharmaceutical preparations is an important parameter governing patient compliance and commercial success in the market. The scope of ion exchange resin for masking the undesirable taste of pharmaceuticals is unlimited. At salivary pH (pH = 6.8), resinates remain in ionized form that make the drug unavailable for the taste sensation. As the formulation enters the upper segment of the GIT, the environment changes to acidic and drug release take place. Polystyrene matrix cation exchange resins have been used to mask the bitter taste of chlorpheniramine maleate, ephedrine hydrochloride and diphenhydramine hydrochloride. Many chewable tablets designed for pediatric or geriatric use have the taste problem of active drug. The ion exchange resin complex offers a method of overcoming the taste problem and offering sustained release. This application is exemplified in the taste masking of pseudoephedrine in the chewable Rondec® decongestant tablet. Pseudoephedrine is absorbed on Amberlite®CG-50, a polymethacrylic acid ion exchange resin (particle size range of 72-147 microns) to a level of 50-60 % drug, using a column procedure (Swarbrick and Boylan, 1988). However, as ion exchange resin could also retard the release of drugs, proper and careful selecting of ion exchange resins are essential to yield optimal taste masking without affecting the bioavailability. Low crosslinkage ion exchange resins are helpful in taste masking in general (Anand et al., 2001).

Four bitter drugs were selected for evaluation in taste coverage studies. They included two with tertiary amine groups (methapyrilene and dextromethorphan) and two with secondary amines (ephedrine and pseudoephedrine). Adsorption onto the

resin reduced the bitterness to some extent. Particle coating give further bitterness reduction. The extent of this reduction is dependent on the coating level. About 25 % of coating level appeared to be sufficient to reduce bitterness (Borodkin and Sundberg, 1971).

### 6.4 Disintegrant

The ion exchange resins swell significantly on exposure to water. This has led to their use as very effective tablet disintegrant. It is usually necessary to use only a few percent of the tablet weight to get complete disintegration within several minutes (Hughes, 2005).

### 6.5 Improve drug stability

The drug resinates are frequently more stable than the original drug. This is exemplified by the stabilization of vitamin B12 in the oldest pharmaceutical resinate application. Vitamin B12 has a shelf life of only a few months, but the resinates are stable for over 2 years. This technology is still used commercially today. Another example is nicotine. Nicotine discolors quickly on exposure to air and light but the resinates are much more stable (Hughes, 2005).

### 6.6 Polymorphism

Polymorphism is a very common problem in the pharmaceutical industry and huge sums money are spent trying to identify polymorphs and trying to make stable, suitably soluble forms. Failure to resolve such problems can result in significant stability problems for the final dosage form. Ion exchange resins present a unique way to deal with the problem. A drug resinate is an amorphous solid that cannot crystallize of even form hydrates. In addition the release of the drug from the resinate is independent of the crystal form that was used to make it. Consequently, using resinates completely eliminates any problems with polymorphism.

Akkaramongkolporn et al (2001) studied about molecular properties of propanolol-resin complex. The molecular state of drug in the complexes was

amorphous, whereas that in the physical dispersion exhibited the crystalline state of pure drug. These results suggested that the molecule of drug prepared as drug-resin complexes was monomolecularly dispersed in the resin bead.

## 7. The release mechanism and kinetics of ion exchange resins

Factors affecting drug release from resinates include the type of ion exchange resins, degree of crosslinkage, particle size, pH of dissolution medium, ionic strength of dissolution medium and counter ion type of dissolution medium (Irwin et al., 1987; Sprockel and Prapaitrakul, 1988). In general, drug is released from the resinates by exchanging with ions in surrounding medium, followed by drug diffusion through the polymer matrix of the resinates. The possible kinetics of the drug release from resinates can be identified into the processes as follow.

### 7.1 Particle diffusion controlled model

This model had been proposed by Baskar et al. (1986). Diffusion of the free drug through the matrix within the resinates could be expressed by the following equation

$$- \ln (1-F) = 1.59( 6/d_p )^{1.3} D^{0.65} t^{0.65} \qquad (11)$$

where F is fractional release of drug from drug resinates, $d_p$ is mean particle size of resin (mm), D is apparent diffusion coefficient or diffusivity ($mm^2/min$) and t is time (min). This model can be investigated by simply testing for linearity between $-\ln (1-F)$ and $t^{0.65}$. The slope of straight line estimated using linear regression analysis was used to calculate the apparent diffusivity according to the following equation.

$$D = \frac{d_p^2}{36} (\text{slope}/1.59)^{1/0.65} \qquad (12)$$

### 7.2 Film diffusion controlled model

This model proposed to test the drug release controlled by aqueous boundary (stagnant) layer of the drug solution around the resinates. Assuming that the thickness of film and distribution coefficient is constant in each resin, the equation used is as follow

$$- \ln (1-F) = 3Pt/d_p \quad (13)$$

where P is apparent permeability of film. The plot between -ln (1-F) and t could provide a linear line with a constant slope, which was used to determine the permeability value (Boyd et al., 1947).

### 7.3 Chemical reaction controlled model

The mathematical model to describe the exchange of the counter ion and the bound drug is displayed below

$$-\ln(1-F) = St \quad (14)$$

where S is the chemical reaction rate constant. The drug release from resinates can be described by the chemical reaction controlled process if the plot between -ln (1-F) and time provides a linear line. The chemical reaction rate constant can be calculated from the slope (Plaizier-Vercammen, 1992).

### 7.4 Matrix diffusion controlled model (Higuchi model)

The common release model is frequently referred to as square-root-of-time or $t^{0.5}$ release, providing compound release that is linear with the reciprocal of the square root of time. The release rate is then given as follow.

$$\frac{dM_t}{dt} = \frac{k}{t^{0.5}} \quad (15)$$

The release model of this type can be described by Higuchi equation (Higuchi, 1963)

$$Q = [D\varepsilon/ \tau(2A-\varepsilon C_s) C_s t]^{0.5} \quad (16)$$

where Q is weight in grams of drug release per unit surface area, D is diffusion coefficient of drug in the release medium, $\varepsilon$ is porosity of the matrix, $\tau$ is tortuosity of matrix, $C_s$ is solubility of drug in the release medium and A is concentration of drug in the tablet, expressed as gm/ml.

The assumptions made deriving equation are as follows:

1. A pseudo-steady state is maintained during release
2. $A>>>C_s$, i.e., excess solute is present
3. The system is in perfectly sink condition in which C, is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix
5. The diffusion coefficient remains constant
6. No interaction between the drug and the matrix occurs

In general Higuchi's equation is usually desired and used as in equation (17)

$$Q = k_h t^{1/2} \quad (17)$$

where $k_h$ is the Higuchi constant. Therefore the plot of amount of drug released from matrix versus square root of time should be increased linearity if drug release from the matrix is diffusion controlled. Although the above equation is based on release from a single face, it may use to describe diffusion-controlled release from all surface matrices.

In order to further verify that the release follows Higuchi model, Higuchi equation is converted into logarithmic form as:

$$\log Q = \log k_h + \tfrac{1}{2} \log t \quad (18)$$

The plot of log Q versus log t must not only yield a straight line, but must have a slope of 0.5.

## 8. Dowex®88 and Dowex®HCR-S ion exchange resin properties

In this study used the polystyrene polymer backbone with divinylbenzene copolymer resins. Dowex®88 and Dowex®HCR-S is the strong cation exchangers contain sulfonic acid site with the sodium counterions absorbed on the resin (Figure 6). Dowex®88 has 4 % crosslinkage and Dowex®HCR-S has 8 % crosslinkage.

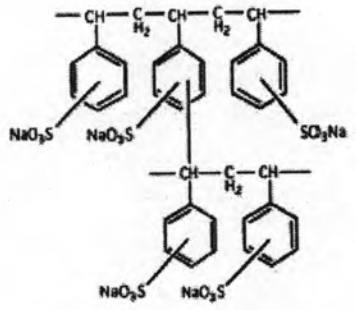


**Figure 6** Chemical structure of sodium polystyrene sulfonate (Takenaga et al.,1998).

## 9. Diltiazem hydrochloride

In this study, diltiazem hydrochloride was used as a model drug. Diltiazem hydrochloride is a calcium ion influx inhibitor or slow calcium channel blocker.

### 9.1 Physicochemical properties (Mazzo et al., 1994)

**Chemical name** (2S-cis)-3-(acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-onemonohydrochloride.

**Empirical name** $C_{22}H_{26}N_2O_4S \cdot HCl$

**Molecular weight** 450.98

**Chemical structure** shows in Figure 7

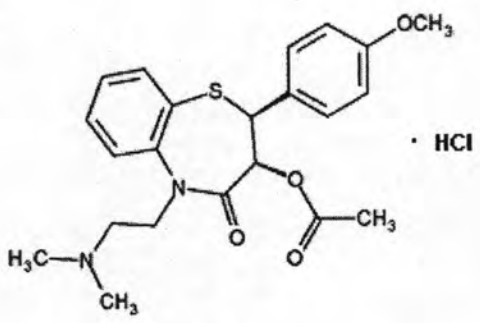



**Figure 7** Chemical structure of Diltiazem hydrochloride (Mazzo et al., 1994).

**Physical properties**

Diltiazem hydrochloride is a white to off-white crystalline power. It is odorless and has a bitter taste. Find needle crystals are obtained from crystallization with ethanol-isopropanol solvent. It has a high melting temperature and melt at approximate 210°C (207.5 – 212°C) with the decomposition at higher temperature.

Diltiazem hydrochloride has not been observed on polymorphic transition form. The saturated solution in aqueous system has a pH value about 3.0. The 1 % w/w solution of diltiazem hydrochloride in purified water has approximate pH at 4.2 while 1 % w/v solution has higher pH value about 4.7.

Dissociation constant (pKa) of diltiazem hydrochloride is equal to 7.7. In addition, liquid-liquid partitioning value or apparent partition coefficient between varying organic solvents to aqueous buffer of n-hexane, dichloromethane, carbon tetrachloride and octanol are 1.0, 4.63, 3.52 and 2.7 respectively.

**Stability**

Diltiazem hydrochloride is high stable in solid state. At ambient temperature and 33 % RH or 79 % RH solid powder is stable in both physical and chemical properties. In elevated temperature (44°C) and high moisture environment (75 % RH), it is stable after three weeks on storage. UV light expose may be a developed powder color changing.

Diltiazem hydrochloride in aqueous system is stable over a pH range of 3-6, especially, optimal point is indicated at pH 5.0 (Mazzo et al., 1994). Won and Iula, (1992) reported the degradation kinetics of diltiazem hydrochloride in various pH was valued follow first order kinetic and undergone with hydrolysis reaction to desacetyldiltiazem. The log k decreased when increasing pH up to pH 4 and increased when increasing pH above pH 4 (Figure 8).

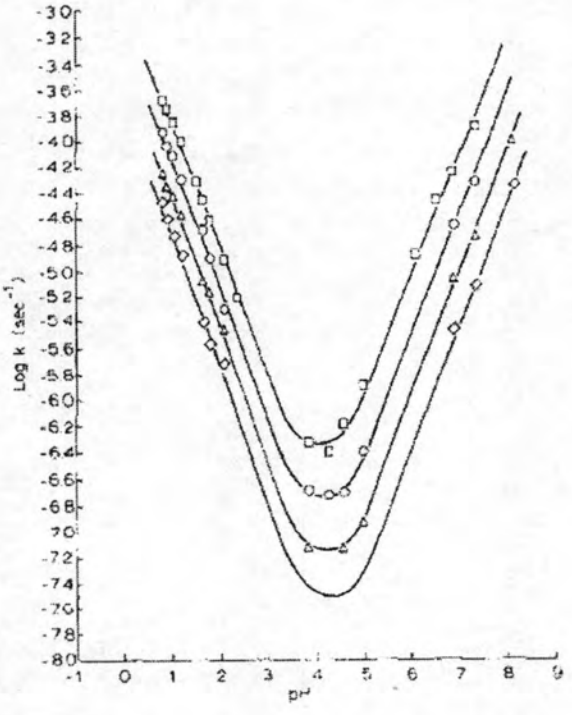



**Figure 8** Log k – pH profiles for the hydrolysis of diltiazem at 50°C (◊), 60°C (Δ), 70°C (○) and 80°C (□). (Won and Iula, 1992).

**Solubility**

Diltiazem hydrochloride is high solubility in various solvents. The solubility of diltiazem hydrochloride in a variety of solvents is presented in Table 3 and in a variety of pH values at 37°C is presented in Table 4.

**Table 3** Solubility of diltiazem hydrochloride in various solvent systems at 25°C

| Solvent | Solubility |
|---|---|
| Chloroform | Freely soluble |
| Formic acid | Freely soluble |
| Methanol | Freely soluble |
| Water | Freely soluble |
| Dehydrated alcohol | Sparingly soluble |
| Benzene | Practically insoluble |
| Ether | Insoluble |

**Table 4** Solubility of diltiazem hydrochloride in various pH values at 37°C (Bodmeier et al., 1996)

| pH values (initial) | pH values (filtrate) | Solubility (mg/ml) |
|---|---|---|
| 1.2 (0.1 N HCl) | 1.2 | 588 |
| 3.5 (phosphate buffer) | 3.46 | 652 |
| 5.0 (phosphate buffer) | 4.87 | 634 |
| 7.4 (phosphate buffer) | 5.82 | 634 |

### 9.2 Pharmacology

Diltiazem hydrochloride is a calcium antagonist effective in treatment of stable, variant and unstable angina pectoris and mild to moderate systemic hypertension, with a generally favorable adverse effect profile. It is also effective in terminating supraventricular tachycardia and in controlling the ventricular response to atrial fibrillation/flutter (AHFS Drug Information, 2003).

### 9.3 Pharmacokinetic

Approximate 90 % of an oral administered dose of diltiazem hydrochloride is absorbed. After administration of single oral dose, including a sustained release

tablets, the mean absolute bioavailability is about 30 to 40 % and is dose related. The area under the plasma concentration-time curve (AUC) increases after multiple dosing, indicating that first-pass metabolism decrease with multiple dosing (AHFS Drug Information, 2003).

### 9.4 Dosage and preparation

Oral dosages in the treatment of systemic hypertension should between 90 to 180 mg/day. Treatment of stable or variant angina pectoris should initiate at 120 mg/day divide with stepwise titration up to a maximum of 360 mg/day. Diltiazem hydrochloride (Cardizem®, Dilacor®) is available as tablets, sustained release capsules and injectable forms. Therapy is individualized and generally begins with 30 mg four times a day up to maximum of 360 mg daily. Intravenous therapy usually begins with a dose of 0.2 mg/kg body weight. Infusions are usually given in dose of 10 mg/hour and can be maintained for up to 24 hours (AHFS Drug Information, 2003).