CHAPTER-III

EVALUATION OF ION-EXCHANGE RESIN IN DRUG DELIVERY
1. Introduction

Ion exchange (IE), particularly base exchange, has been the subject of several scientific investigations since the middle of the 20th century. In the beginning it was primarily a significant process in the field of agriculture and organic analytical chemistry, which later attracted research by healthcare professionals into this subject. Until 1934, natural and synthetic siliceous materials, known as zeolites, were able for use as IE adsorbents for purification of water (Mantell 1951). In 1934, Adams and Holmes synthesized phenol-formaldehyde resin and showed that this resin can be used as a substitute for zeolites. In fact, it paved the way for application of IER to several industrial processes and biomedical application (Adams and Holmes 1935). But it was not until 1950, that IER were studied for pharmaceutical and biomedical applications. At this time, Chaudhury & Saunders (1956) studied the uptake and release of alkaloids from IER and suggested that these resins might act as a suitable chemical carrier for the development of sustained-release formulations. IER have since been extensively explored in the field of drug delivery including controlled release, transdermal, site specific, fast dissolving, iontophoretically assisted transdermal, nasal, topical, and taste masked systems.

Chemically, IER are made up of two components: a structural component consisting of the polymer matrix, and a functional component to which the counter ion is bound. The structural component of IER consists of a stable acrylic polymer of styrene-divinylbenzene copolymer, whereas the functional component can be acidic (commonly sulfonic or carboxylic) or basic (amine). These functional components called exchangeable groups are exchanged by same charged ion through simple adsorption process. Moreover based on the nature of the ionic species being interchanged, the IE process is known as either cation exchange (CE) or anion exchange (AE). The IER used in these processes are referred to as cation-exchange resin (CER) or anion-exchange resin (AER) respectively. The process is competitive in nature.

In practice, drug in an ionic form (usually in solution) is mixed with the appropriate IER either by batch (after suitable pretreatment, a specific quantity of the granular IER is agitated with the drug solution until the equilibrium is established)(Sanghavi, et al., 1988) or column (a concentrated solution of drug is passed through the IER-packed column until the effluent concentration is the same as the eluent
concentration) technique to form a complex, known as ‘resinate’. The following steps are involved in the preparation of resinates:

- Purification of resin by washing with absolute ethanol or methanol. Final washing is done with water to remove all the impurities.
- Change of the ionic form of IER might occasionally be required to convert a resin from one form to another, if it does not have the desired counter ions (Jeffery et al. 1989).

The performance of resinate is governed by several factors as:

- The pH and temperature of the drug solution;
- The molecular weight and charge intensity of the drug and IER;
- Geometry;
- Mixing speed;
- Ionic strength of the drug solution;
- Degree of cross linking and particle size of the IER;
- The nature of solvent; and
- Contact time between the drug species and the IER (Jenke, 1989; Irwin and Belaid, 1987; Burke et al., 1986; Plaizier-Vercammen, et al., 1992)

The interactions between the IER and drug, although primarily chemical in nature, are also partially a result of physical adsorption (Wallwork 1956). When the resinate from the delivery system reaches the site of delivery, the exchange process is reverted, resulting in the liberation of free-drug ions. Therefore the ionic strength and pH at the site of delivery play a key role in the liberation of the immobilized drug from the resinate. Drug delivery at the desired target via the IE process occurs because of the presence of highly activated counter ions at the site, resulting in the exchange of ions and drug release. The IER devoid of drug is eliminated or biodegraded from or at the site of delivery (Hui et al. 1987). Fig. 1. depicts the factors that affect the IE process involved in the delivery of a cationic drug.
In vitro formulation environment | In vitro drug release and absorption environment | In vitro formulation (after drug absorption)
---|---|---
![Diagram](image)

**Complexation and formation**
- Ion-exchange capacity
- Particle size of the resin
- Size of drug ion
- Drug solubility
- \(pH\) and ionic strength
- Temperature

**drug release and absorption**
- Ionic strength and \(pH\)
- Crosslinking of resin
- Drug solubility
- Binding sites
- Membrane permeability
- at the site

**Excretion and elimination**
- Biodegradation and biocompatibility
- Site of administration

Figure 1. The basis of the ion-exchange process in the drug delivery with factors affecting the therapeutic efficacy of the system at each stage. R and a green circle represent resin; - sign depicts the integral ion of the resin and \(A^+\) is the counter ion. D is the drug ion. \(X^-\) is the ion associated with drug cation and \(H^+\)\(\text{Cl}^-\) is the hydrochloric acid. Ions inside and outside the resin indicate ions adsorbed at the surface, as well as at the interior, of the resin structure.

The selection of IER for drug delivery applications is primarily governed by the functional group properties of IER (Saunders 1953). 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 milliequivalents 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; and
• Regulatory status of the IER.
• Porosity and moisture content.

For example, the use of a strong IER will give a rapid rate of exchange, but it also causes hydrolysis of the labile drugs because strong IER are effective acid-base catalyst. Therefore, a fine balance of all the parameters needs to be made to achieve optimal performance of drug-delivery systems (DDSs) containing IER.

The scope of IER for masking the unpleasant taste of pharmaceuticals is unlimited. CER have been successfully used to mask the bitter taste of chloroquine phosphate (Agarwal, et al 2000), chlorpheniramine maleate, ephedrine hydrochloride, diphenhydramine hydrochloride (Manek and Kamat 1981). Bryan et al (1967) studied on palatable antitusive agent-resin complex. Lu et al (1991), Lu and Borodkin (1989) described the application of a polyacrylic acid complex to overcome the bitter taste of erythromycin and other macrolides. Borodkin and Sundberg (1971) applied weak cation-exchange resin for taste masking of pseudoephedrine in the chewable Rondec decongestant tablet. Generally, less cross-linked IER are helpful in taste masking (Nanda et al., 2002). Resinates can also be used to provide decreased toxicity (Abraham & Linnell, 1957) and enhanced stability profiles (Keating, 1961). Drug release from the resinate relies on the ionic environment and should therefore be less susceptible to other conditions such as enzyme content, at the site of absorption (Hui et al 1987). Abrahams and Linnell (1957) stated that the rate at which a drug resin salt decomposes depends entirely on the ion strength of the gastrointestinal fluids and not on the action of enzymes and other physiological factors. Therefore, the suitability of IER approach to drug delivery depends on the route and target of delivery. Moreover, resinates alone are the simplest forms of controlled- or sustained-release drug delivery systems. So peroral controlled- and sustained-release DDSs have been widely studied with this approach,
because the ionic environment of the gastro-intestinal tract (GIT) is suitable for the exchange process. The IE process might not be applicable to the skin, external canals (e.g. nasal and ear), or other areas with limited quantities of eluting ions. In contrast, the subcutaneous and intramuscular routes, where the pool of ions is more controlled, would appear better suited for this approach. The use of IER has occupied an important place in the development of controlled- or sustained-release drug delivery systems because of their drug-retaining properties and prevention of dose dumping. The polymeric (physical) and ionic (chemical) properties of IER will release the drug more uniformly than that of simple matrices (because of physical properties only) (Chaudhury & Saunders, 1956). Besides the use of ion-exchange resinate as sustained /controlled drug delivery device, many dosage form like matrix tablets (Sanghavi et al 1988), beads (Motycka and Narin 1978), capsules (Deeb and Becker 1960), suspension (Borodkin 1976), ointments (Fiedler and Sperandio 1957) have been developed using resinate.

Hamlow et al (1956) reported that morphine is more readily released from carboxylic resin in neutral or alkaline medium than acidic medium.

Chaudhry and Saunders (1956) studied the release of ephedrine from sulphonated cross-linked polystyrene resins in 0.1 N HCl under static and dynamic conditions.

Freed et al (1956) concluded on the basis of clinical tests that amphetamine is released from sulphonic acid amphetamine resinates on a predictable basis for a period of 10 to 14 hr.

The prolonged activity of ointments containing two antibacterial drugs (neomycin and sulfadiazine) adsorbed on a carboxylic acid cation exchange resin and on strongly basic anion exchange resin, respectively, was studied by Fiedler and Sperandio (1957). Bacteriological testing showed that resinate exhibited a prolonged effect compared with their free drug counterparts.

Cass and Frederik (1958) demonstrated a prolonged activity of sulphonylic acid type resinates containing the antitussive phenyltoloxamine or a mixture of phenyltoloxamine and dihydrocodeinone by in vitro and in vivo experiments.

Swift (1960) studied the duration of action of salts of antihistaminics, such as pyrilamine, phenyltoloxamine, tripelennamine and chlorpheniramine, with powdered or granular sulphonylic acid type cation exchange resines. He also reported that the particle
size of the resinate appeared to be very important in the duration of action and a satisfactory prolonged effect (30hr) without increasing dose could be obtained by mixing resinates of powered phenyltoloxamine and granular chlorpheniramine. In addition, the side effects typically produced by antihistaminics were diminished.

Wulff (1965) compared the duration of antitussive effect of noscapine hydrochloride loaded on a sulfonated cross-linked polystyrene resin (4% cross-linked, 200-400 mesh, and containing 62 to 64% w/w drug). By means of experimentally induced cough in guinea pigs, a significant reduction of cough attacks was observed with the resin-bound drug for more than 5 hr.

Rety et al (1963) and Saunders (1961) achieved a prolonged action of barbiturates in the body by preparing resinate with anion exchange resin and showed that suitable cross-linking of the resin was necessary for prolongation of action.

Lichtneckert et al (1975) developed a flavored chewing gum containing nicotine absorbed on a carboxylic acid ion exchange resin.

Jayaswal and Bedi (1980) reported propranolol resinates from weak and strong cation exchange resin as a very promising sustained released system by in vivo experiments. He studied the percent blocked of the isoprenaline-induced tachycardia after oral administration of a plain marketed sample of propranolol and a resinate mixture of propranolol in anesthetized dogs. Following oral administration of plain tablets 35% β-blocking activity was noticed after 30 min. A maximum activity of 46% β-blocking occurring after 4 hr while a 27% was observed at the 7th hr. In the case of resinate formulation, a distinct β-blocking activity (50%) was observed as early as 30 min after oral administration. The blockade maxima (72 to 73%) were observed between 4th to 8th hour and 70% of blockade still remained at 9th hr. These results emphasize once more the potentiality of drug-resin complex as formulations with prolonged release characteristics.

Gyselinck et al (1981) and Schacht et al (1982) investigated the influence of cross-linking density and size of resin on the maximal drug content and release rate of resinate prepared with three amine drugs (levamisol, procainamide and propranolol) with sulphonic acid type cation exchange resin (Dowex® 50W). As the the degree of cross-linking increased, both the drug content and release rate decreased, however, the particle size are less straightforward in that respect. They also compared the resinate of
procainamide and Dowex® 50W (X 12, 100-200 mash) with the commercial “retard” preparation, Durettew® and concluded that although the resorption of procainamide was somewhat irregular (irrespective of dosage form), the performance of the resinate was superior to that of the pure drug and was as efficient as the Durettew®.

Burke et al (1986) investigate the application of six strongly acidic cation exchange resins (Amberlite XE-364R, IRP-69, IR-120 and IR-122a, Dowex 50W X4 and X8b) as a sustained drug delivery system of propranolol hydrochloride and they have concluded that propranolol complexed with strongly acidic cation exchange resins is an effective sustained drug delivery system itself.

Bhaskar et al (1986) developed a novel-method to evaluate the release mechanism of metoclopramide loaded on Amberlite IL-120 cation exchange resin.

Irwin et al (1987) observed the important role of different variables like particle size, pH of medium, stirring speed, cross-linking, ionic strength on loading efficiency and release behavior of resinate prepared with a series of o-n-acyl propranolol prodrugs and strong cation exchange resins like Dowex 50WX8 and Amberlite. They also described the loading and release of ibuprofen, ketoprofen and mefenamic acid from a range of strong anion exchange resin Dowex with different cross-linking and particle size (Irwin et al 1990).

From the above cited research articles it appeared that majority of the studies on ion-exchange resins and the different dosage forms prepared thereof are limited to various type of Amberlite and Dowex resins. To the best of our knowledge, Indion 254®, a cation exchange resin, has not been studied with respect to its sustained release properties. The objective of this part of the work was, therefore, to study different parameters involved in the formation of drug-Indion 254® resin complex and to evaluate the resinate for sustained release properties. Diltiazem hydrochloride and propranolol hydrochloride have been selected as water soluble drugs to evaluate the resin with respect to its sustained release properties.
2. Materials

2.1. Raw Materials:

<table>
<thead>
<tr>
<th>Materials</th>
<th>Grade</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem hydrochloride</td>
<td>Indian Pharmacopoeia</td>
<td>M/s. Stadmed Ltd., Kolkata, India</td>
</tr>
<tr>
<td>Propranolol hydrochloride</td>
<td>Indian Pharmacopoeia</td>
<td>M/s. Sun Pharmaceutical Industries Ltd., Gujarat, India</td>
</tr>
<tr>
<td>Indion 254®, sulphonlic acid cation exchange resin in Na⁺ form</td>
<td>Pharmaceutical grade</td>
<td>Ion Exchange (India) Pvt. Ltd., Mumbai, India</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Laboratory Reagent</td>
<td>E. Merck (India); Mumbai, India</td>
</tr>
<tr>
<td>Sodium hydroxide pellets</td>
<td>Laboratory Reagent</td>
<td>Quest Chemicals.; Kolkata, India</td>
</tr>
<tr>
<td>Potassium dihydrogen-orthophosphate</td>
<td>Analytical Reagent</td>
<td>Qualigens® Fine Chemicals.; Mumbai, India</td>
</tr>
<tr>
<td>Citric acid</td>
<td>Laboratory Reagent</td>
<td>Quest Chemicals.; Kolkata, India</td>
</tr>
<tr>
<td>Deionised water</td>
<td>Complies with purified water I.P.</td>
<td>D.I. Laboratories.; Kolkata, India</td>
</tr>
</tbody>
</table>

3. Methods:

3.1. Determination of wavelength of maximum absorbance ($\lambda_{\text{max}}$) of diltiazem hydrochloride in deionised water:

25 mg of drug was dissolved in deionized water and volume was made up upto 50 ml. 0.5 ml of the solution was further diluted to 25 ml with deionized water and the solution was scanned from 190 – 350nm in UV-VIS double beam spectrophotometer (Hitachi, 200-20, Japan) using deionised water as blank under the following conditions; slit width = 2.0 nm, scan speed = 60 nm/min and O.D. = 0-2. The wavelength of maximum absorbance ($\lambda_{\text{max}}$) for diltiazem hydrochloride was found to be 236 nm (Fig. 1).
Fig. 1. Ultraviolet spectrum of diltiazem hydrochloride in deionized water.

3.2. Determination of wavelength of maximum absorbance ($\lambda_{\text{max}}$) of propranolol hydrochloride in deionised water:

The wavelength of maximum absorbance of propranolol hydrochloride was determined following the same method described in 3.1 and was found to be 290 nm (Fig. 2).
3.3. Calibration curve for diltiazem hydrochloride in deionised water:

25 mg of accurately weighed diltiazem hydrochloride was dissolved in deionized water and the volume was made up to 50 ml. From the stock solution 0.1, 0.2, 0.4, 0.5, 0.6, 0.8 and 1.0 ml were taken in 25 ml standard volumetric flask and diluted by the deionized water up to the mark and the absorbances were measured at 236 nm using the deionized water as blank. This experiment was triplicated. The average values of absorbances were plotted against respective concentrations (Fig. 3).
Fig. 3. Calibration curve for diltiazem hydrochloride in deionised water.

3.4. Calibration curve for propranolol hydrochloride in deionised water:

The calibration curve for propranolol hydrochloride was constructed at 290nm following the same method described in 3.3. (Fig. 4).

Fig. 4. Calibration curve for propranolol hydrochloride in deionised water.
3.5. Preparation HCL solution of pH 1.2:

8.33 ml 12 (N) HCl was mixed with 991.66 ml distilled water and the pH was adjusted at 1.20.

3.6. Determination of wave length of maximum absorbance ($\lambda_{\text{max}}$) of diltiazem hydrochloride in HCl solution (pH 1.2):

The wave length of maximum absorbance of diltiazem hydrochloride in HCl solution (pH 1.2) was determined following the method described in 3.1 and was found to be 236 nm (Fig. 5).

Fig.5. Ultraviolet spectrum of diltiazem hydrochloride in 0.1 (N) HCL solution.
3.7. *Determination of wave length of maximum absorbance (λ\text{max}) of propranolol hydrochloride in HCl solution (pH 1.2):*

The wave length of maximum absorbance of propranolol hydrochloride in HCl solution (pH 1.2) was determined following the same method described in 3.1 and was found to be 290 nm (Fig. 6).

![Ultraviolet spectrum of propranolol hydrochloride in 0.1 (N) HCL solution.](image)

3.8. *Calibration curve for diltiazem hydrochloride in 0.1 (N) HCL solution:*

The calibration curve for diltiazem hydrochloride was constructed at 236nm following the same method described in 3.3. (Fig. 7)
3.9. Calibration curve for propranolol hydrochloride in 0.1 (N) HCL solution:

The calibration curve for propranolol hydrochloride was constructed at 290nm following the same method described in 3.3. (Fig. 8)

3.10. Preparation of phosphate buffer of pH 7.2 and 6.8:

The phosphate buffer solution of pH 7.2 and 6.8 were prepared following the method described in US Pharmacopoeia (1990a).
3.11. Determination of wave length of maximum absorbance \((\lambda_{\text{max}})\) of diltiazem hydrochloride in phosphate buffer of pH 7.2:

The wave length of maximum absorbance of diltiazem hydrochloride in phosphate buffer of pH 7.2 was found to be 236 nm as determined following the same method described in 3.1 (Fig. 9).

---

**Fig. 9.** Ultraviolet spectrum of diltiazem hydrochloride in phosphate buffer of pH 7.2.
3.12. Determination of wave length of maximum absorbance ($\lambda_{\text{max}}$) of propranolol hydrochloride in phosphate buffer of pH 6.8:

The wave length of maximum absorbance of propranolol hydrochloride in phosphate buffer of pH 6.8 was found to be 290 nm as determined following the same method described in 3.1 (Fig. 10).

Fig.10. Ultraviolet spectrum of propranolol hydrochloride in phosphate buffer of pH 6.8.
3.13. Calibration curve for diltiazem hydrochloride in phosphate buffer of pH 7.2:

The calibration curve for diltiazem hydrochloride was constructed at 236nm following the same method described in 3.3. (Fig.11).

![Fig.11. Calibration curve for diltiazem hydrochloride in phosphate buffer of pH 7.2.](image)

3.14. Calibration curve for propranolol hydrochloride in phosphate buffer of pH 6.8:

The calibration curve for propranolol hydrochloride was constructed at 290nm following the same method described in 3.3. (Fig.12).

![Fig.12. Calibration curve for propranolol hydrochloride in phosphate buffer of pH 6.8.](image)
3.15. Preparation of McIlvaine phosphate-citrate buffer of pH 3:

A McIlvaine phosphate-citrate buffer of pH 3 with different ionic strengths was prepared by using Potassium dihydrogen-orthophosphate and citric acid (Elving et.al.; 1956).

3.16. Determination of wave length of maximum absorbance ($\lambda_{max}$) of diltiazem hydrochloride in McIlvaine phosphate-citrate buffer of pH 3:

The wave length of maximum absorbance of diltiazem hydrochloride in McIlvaine phosphate-citrate buffer of pH 3 was found to be 236 nm as determined following the same method described in 3.1 (Fig. 13).

Fig.13. Ultraviolet spectrum of diltiazem hydrochloride in McIlvaine phosphate-citrate buffer of pH 3.
3.17. Determination of wave length of maximum absorbance ($\lambda_{max}$) of propranolol hydrochloride in McIlvaine phosphate-citrate buffer of pH 3:

The wave length of maximum absorbance of propranolol hydrochloride in McIlvaine phosphate-citrate buffer of pH 3 was found to be 290 nm as determined following the same method described in 3.1 (Fig. 14).

Fig.14. Ultraviolet spectrum of propranolol hydrochloride in McIlvaine phosphate-citrate buffer of pH 3.
3.18. *Calibration curve for diltiazem hydrochloride in McIlvaine phosphate-citrate buffer of pH 3:*

The calibration curve for diltiazem hydrochloride was constructed at 236nm following the same method described in 3.3. (Fig.15).

![Fig.15. Calibration curve for diltiazem hydrochloride in McIlvaine phosphate-citrate buffer of pH 3.](image)

3.19. *Calibration curve for propranolol hydrochloride in McIlvaine phosphate-citrate buffer of pH 3:*

The calibration curve for propranolol hydrochloride was constructed at 290 nm following the same method described in 3.3. (Fig.16).

![Fig.16. Calibration curve for propranolol hydrochloride in McIlvaine phosphate-citrate buffer of pH 3.](image)
3.20. Activation of resin:

Sulphonic acid cation exchange resin was stirred in 200 ml deionized water with a magnetic stirrer for 1h and left aside to settle down. The resin was separated by decantation and washed consecutively with methanol (2x50ml) to remove impurities. The resin was then activated by recycling alternately thrice with 1(M) NaOH (60 ml) and 1 (M) HCl (60 ml) and washing after each treatment with deionized water. Finally the resin in hydrogen/acid form was washed with deionized water until the elute was neutral. The resin was then vacuum dried at 50°C to constant weight. The dried resin was fractionated into 100-200, 240-300 and 300-350 mesh by sieving through a nest of British Standard sieves.

3.21. Determination of cation exchange capacity of resin:

The total capacity of cation exchange resin was determined by converting it to the hydrogen form, and then a neutral sodium salt was added to displace the hydrogen ions which were titrated as free acid.

1. About 0.5 gm of the resin in Na form was accurately weighed and transferred into a 100 ml beaker. 25 ml deionized water was added.
2. About 2 gm of Analar sodium chloride was added with stirring.
3. The mixture was titrated with 0.1 (N) NaOH solution using methyl orange indicator.
4. The end point was reversed several times during titration, however, a steady end point was obtained within a reasonable time.

\[
\text{Dry weight cation exchange capacity of resin} = \frac{TN}{W} \text{ meq/dry g}
\]

where, weight of dry resin = Wg, normality of NaOH solution = N and Titre = T ml.

3.22. Preparation of diltiazem-resin complex:

Diltiazem-resin complex (resinate) was prepared by batch process. About 100mg of resin, accurately weighed, was stirred with drug solution having known concentration for 3 h. Resinate was separated by vacuum filtration and washed with deionized water till the filtrate showed no absorbance at 236 nm for diltiazem. The filtrate and the washings
were pooled and kept aside for analysis of residual drug. Resinates were dried at 50\(^0\)C in vacuum to constant weight. The following parameters were varied:

1. Stirring time : 5 to 180 min  
2. Drug concentration : 0.33 to 1.2 mg/ml  
3. Size of the resin : 100-200 mesh, 240-300 mesh and 300-350 mesh  
4. Loading temperature : 30\(^0\)C and 100\(^0\)C

3.23. Preparation of propranolol-resin complex:

Propranolol-resin complex (resinate) was prepared following the method in 3.22.

3.24. Drug content of resinate:

The amount of drug loaded in the resin was determined by three methods –

(1) Subtraction method (Akkaramong Kolporn et al., 2001) – The pooled filtrate and washings was analyzed spectrophotometrically (Hitachi 200-20, Japan) at 236 nm and 290nm for diltiazem and propranolol hydrochloride respectively. The amount of drug bound in the resin was calculated from the concentration difference of the drug between the initial drug solution and the pooled filtrate.

(2) Desorption method (Torres et al., 1998) – About 60 mg, accurately weighed, resinate was stirred with a magnetic stirrer in 200 ml NaCl-HCl buffer (pH 1.3) at 30\(^0\)C. The buffer was replaced every hour upto 5 h. The solutions from each sample were accumulated and analyzed, following dilution if necessary, spectrophotometrically at 236 nm and 290nm for diltiazem and propranolol hydrochloride respectively.

(3) About 20mg, accurately weighed, resinate was shaken for 48 h in 250 ml USP phosphate buffer solution (pH 6.8 for propranolol and pH 7.2 for diltiazem) and then filtered. The filtrate, following suitable dilution, was assayed spectrophotometrically (Hitachi, 200-20, Japan) at 236nm and 290nm for diltiazem and propranolol hydrochloride respectively.

3.25. Diltiazem release study:

In-vitro release of diltiazem hydrochloride from resinate was monitored in HCl solution (pH 1.2) and phosphate buffer (pH 7.2) at 37\(\pm\)1\(^0\)C using programmable dissolution tester (paddle type, Electrolab, model TDT-06P (USP), India) at respectively 100 and 50 rpm. Aliquots were removed at predetermined times and were replenished
immediately with the same volume of fresh media. The aliquots, following suitable
dilution, were assayed spectrophotometrically at 236 nm.

3.26. Propranolol release study:

In-vitro release of propranolol hydrochloride from resinate was monitored following
the method in 3.25.

4. Results and Discussion:

4.1. Equilibrium study:

Drug resin complex were prepared by batch process where a known amount of
resin was stirred in the solution of the drug and periodically the drug solution was
analyzed. The fractional attainment of diltiazem and propranolol have been presented
respectively in Figure 17 and Figure 18. The amount of diltiazem adsorbed onto the resin

![Graph showing fractional attainment of equilibrium for diltiazem at different temperatures and resin sizes.]

Fig. 17. Effect of temperature and size of cation exchange resin on fractional attainment of equilibrium of diltiazem. Key - (◆) 100-200 mesh at 30°C, (●) 240-300 mesh at 30°C, (▲) 300-350 mesh at 30°C and (■) 100-200 mesh at 100°C.
increased rapidly at the initial moment then slowly with time and finally reached the equilibrium. Similar adsorption phenomenon was observed for propranolol. At the initial moment the drug was predominantly adsorbed onto the active sites present on the surface of the resin particles. With time the resin particles also swell allowing more drug ions to enter into the interior of the resin particles. Similar increase in uptake of sulphadiazine sodium by Dowex 1x8 (Cl⁻) and chlorpheniramine by Amberlite CG 50 have been reported (Kondo et al 1996; Spockel and Price 1990). After reaching the equilibrium concentration, there was no further increase in drug adsorption. No further increase in adsorption was not because of the saturation of the active sites of the resin particles. The exchange capacity of the resin determined experimentally, was found to be 3.8 meq/gm of resin; whereas diltiazem and propranolol occupied respectively 1.21 and 1.91 meq/gm of resin at equilibrium. The attainment of equilibrium before saturation of active sites may be due to increase competition between the ionized drug and the hydrogen ions produced through exchange from the active sites. In addition, molecular weight of the drugs might also be an determinant factors. It has been reported that larger cations are unable to penetrate the smaller pores of resin particles.

Fig. 18. Effect of temperature and size of cation exchange resin on fractional attainment of equilibrium of propranolol. Key - (◆) 100-200 mesh at 30°C, (●) 240-300 mesh at 30°C, (▲) 300-350 mesh at 30°C and (■) 100-200 mesh at 100°C.
The attainment of fractional equilibrium was found to be influenced by the size of the resin particles and the temperature of equilibrium study. The smaller the size of the resin, the faster is the attainment of equilibrium. Figure 17 shows that equilibrium concentration of diltiazem was achieved in 3 h when the size of the resin particles was 100-200 mesh. On the other hand, with 240-300 mesh and 300-350 mesh resin particles, the equilibrium concentrations of diltiazem were attained respectively at 50 min and 30 min. Similar observation were noted with propranolol (Figure 18) although the time required to reach equilibrium were different from those required for diltiazem. The smaller the size of resin particles, the greater the number of exposed active sites. This results in rapid attainment of equilibrium.

To study the effect of temperature on the fractional attainment of equilibrium, the equilibrium study was conducted at 30°C and 100°C using 100-200 mesh resin. From the Figures 17 and 18 it is evident that at higher temperature, the time required for the attainment of equilibrium concentrations was less for both the drugs. This was due to the expansion of the resin by heat affording ions to enter into the deeper exchange sites (Irwin et al 1987; Irwin et al 1990).

The amount of diltiazem and propranolol hydrochloride bound in the resin (100-200 mesh) increased as the initial drug concentration in the charging solution was increased, reached a maximum and then, became almost constant (Figure 19). Kondo et al (1996) reported that the percentage of drug reacted increased as the drug concentration
increased and when the drug resin/ratio was greater than 2:1, only a slight increase in percentage of the reacted drug with increase drug concentration was observed. Similarly, Sriwongjanya and Bodmeier (1997) reported that the loading capacity of chlorpheniramine maleate, propranolol HCl and pseudoephedrine HCl on Amberlite® IRP 69 (Na⁺) increased with increasing amount of drug in the external phase during the loading and then leveled off. As the drug concentration increases, the concentration of counter ions produced through exchange also increases. This phenomenon, in conjunction with reduced number of binding sites, increases competition between the ionized drug and hydrogen ions for the remaining sites (Spockel and Price 1990). Further, the initially swollen ionized form of resin shrinks upon contact with aqueous solution of electrolyte and the degree of shrinking being greater as the external solution becomes more concentrated with electrolyte (Boyd et al. 1947). These resulted in decreased adsorption efficiency at higher drug concentration.

4.2. Drug content of the resinate:

The amount of drug loaded in the resinate was determined by three methods. The values obtained from the desorption methods were consistently lower than those obtained from subtraction method. Since the maximum difference in values obtained from three
methods was less than 5%, the value obtained from the subtraction method was considered as the method of choice for content determination for simplicity and rapidity.

The amount of diltiazem loaded in the resin at equilibrium has been represented in Table 1. Diltiazem content was found to depend on the size of resin.

Table 1

Comparison of Subtraction method with desorption methods for diltiazem content in resinate having different size and prepared at different temperatures.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Size range of resin (mesh)</th>
<th>Diltiazem Content (% W/W, ± S.d., n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Subtraction method</td>
</tr>
<tr>
<td>30°C</td>
<td>100-200</td>
<td>56.02(±1.27)</td>
</tr>
<tr>
<td></td>
<td>240-300</td>
<td>61.87(±1.01)</td>
</tr>
<tr>
<td></td>
<td>300-350</td>
<td>64.55(±0.89)</td>
</tr>
<tr>
<td>100°C</td>
<td>100-200</td>
<td>63.01(±1.01)</td>
</tr>
</tbody>
</table>

As the size of the resin decreased, the amount of diltiazem in the resinate increased. Similar increase in propranolol content with decrease in size of the resin was evident (Table 2). With a view to ascertaining that the drug content in the resinate differed

Table 2

Comparison of substitution method with desorption method for propranolol content in resinate having different size and prepared at different temperatures.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Size range of resin (mesh)</th>
<th>Propranolol Content (% W/W, ± S.d., n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Subtraction method</td>
</tr>
<tr>
<td>30°C</td>
<td>100-200</td>
<td>59.23(±0.61)</td>
</tr>
<tr>
<td></td>
<td>240-300</td>
<td>62.33(±1.30)</td>
</tr>
<tr>
<td></td>
<td>300-350</td>
<td>65.89(±1.12)</td>
</tr>
<tr>
<td>100°C</td>
<td>100-200</td>
<td>74.08(±1.19)</td>
</tr>
</tbody>
</table>

with resin size, statistical analysis, in the form of one criteria classification of analysis of variance (ANOVA) of the amount of diltiazem loaded on different sized resins was conducted. The result showed significant difference (P<0.05). Similar observations were noted with propranolol content. Smith et al (1959) reported that the effect of particle size of resin on equilibrium drug content is less pronounced, except for highly cross-linked
resins where the drug content increases as the resin size decreases. Other workers also reported drug loading to be independent of the size of the resin (Burke et al. 1986; Irwin et al. 1987; Irwin et al. 1990). In the present study, it appears reasonable to state that as the size of resin particles decreases, the diffusional path length decreases and the number of exposed active sites increases. These factors increase the amount of drug bound onto the resin. Increase in the temperature of drug loading also increased the amount of drug adsorbed onto the resins at equilibrium (Tables 1 and 2). Increase in loading temperature from 30°C to 100°C increased the diltiazem content from 56.02% to 63.01% and propranolol content from 59.23% to 74.08%. Ketoprofen loading on Dowex 8-50 resins has been reported to increase from 24.90% at 22°C to 35.70% under reflux condition. The increase in drug loading due to increase in loading temperature has been attributed to the expansion of resins by heat affording more drug ions to enter into the dipper exchange sites of resins (Irwin et al. 1987; Irwin et al. 1990).

4.3. Drug release from resinate:

The release profiles of diltiazem from resinate in different dissolution media have been shown in Figure 20. The release profiles in the two media appeared to be superimposable indicating that drug release from the resinate was pH independent. Since

![Figure 20](image)

**Fig. 20.** Effect of the size of resin on diltiazem release from resinate in pH 7.2 (closed symbols) and pH 1.2 (open symbols). Key – (■) 100-200 mesh, (▲) 240-300 mesh, (●) 300-350 mesh.
the two dissolution media contained varying counter ions in different concentrations, such insignificant effect of the two dissolution media on diltiazem release appears to be ambiguous, although it has been stated that pH independent release is a characteristics of resinates. Various workers have, however, reported drug release to be dependent on the pH of dissolution media. Irwin et al (1987) reported a small difference in propranolol release from weak Amberlite resin at pH 1.6 and 7.4. Sprockel et al (1990) reported that hydrogen ions causes faster drug release from resinates than sodium and calcium ions. Kondo et al (1996) also observed higher sulphadiazine release is simulated gastric fluid than that in simulated intestinal fluid. Similar observation have been reported by Atyabi et al (1996).

The release profiles of propranolol from the resinates in the two dissolution media have been shown in Figure 21. The release of propranolol from the resinate having 240-300 and 300-350 mesh size were pH independent. Surprisingly, the drug release from the bigger resinate was influenced by the pH of the dissolution media. t_{50\%} and t_{80\%} (time required for respectively 50\% and 80\% drug release) in pH 1.2 was significantly lower (p<0.05) from those in pH 6.8.

![Fig. 21. Effect of size of resin on propranolol release from resinates in pH 6.8 (closed symbols) and pH 1.2 (open symbols). Key – (■) 100-200 mesh, (▲) 240-300 mesh, (●) 300-350 mesh.](image-url)
The release of both diltiazem and propranolol were found to be dependent on the size of resin particles. The smaller the resin size, the faster was the drug release. For a given weight of resin, as the size decreases, the diffusional path length decreases as well as the drug-bound active sites remain more exposed which leads to rapid ion-exchange and consequently faster release (Figure 20 and 21). The effect of resin size on drug release have been reported by several workers (Raghunathan et al 1981; Irwin et al 1987; Irwin et al 1990).

The effect of temperature of resinate preparation on drug release was studied using 100-200 mesh resin and the results have been represented in Figure 22 and 23. The resinates which were prepared at higher temperature (100°C) discharged the drug more slowly than the resinates which were prepared at lower temperature (30°C). This was true for the release of both diltiazem and propranolol. At elevated temperature, the resin particles expand allowing drug ions to enter into the deeper sites. On cooling the resin relaxes entrapping the drug and provides greater diffusional resistance to elusion/release of drug (Irwin et al 1990).

![Graph showing the effect of temperature on diltiazem release from resinates (100-200 mesh) in pH 7.2](image)

Fig. 22. Effect of temperature on diltiazem release from resinates (100-200 mesh) in pH 7.2 Key – (●) 100°C and (▲) 30°C.
To investigate the effect of ionic strengths on drug release from the resinate (100-200 mesh), the release study was conducted in McIlvaine buffer (pH 3) having different ionic strengths. The ionic strengths were varied from 0.05 to 0.15 for diltiazem and from 0.05 to 0.5 for propranolol. The effect of ionic strengths on release of the drugs have been represented in Table 3 in terms of dissolution efficiency parameters (DEPs) which were calculated following the method of Khan and Rhodes (1972). The results show that increase in ionic strengths increased the release of both drugs significantly (P<0.05) as evident from increase in DEPs. However, increase in ionic strength did not increase the
release of diltiazem appreciably. This was probably due to higher equilibrium of the drug as evident from quick attainment of fractional equilibrium during the adsorption study. This is possible because Raghunathan et al (1981) reported that 4 fold increase in ionic strength increased the release of chlorpheniramine, a drug having low equilibrium concentration, by 64.5% whereas the release of phenylpropanolamine, a drug having high equilibrium concentration, was increased by only 16%.

4.4. Kinetics of adsorption and desorption study:

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 process have been mainly concerned with equilibrium rather than with kinetics. This is understandable since most studies deal with the exchange of small ions, in which the equilibrium is reached fairly rapidly. For large organic ions the equilibrium is reached only very slowly and kinetic consideration are important. In the exchange process one counter ion must migrate from the solution into the interior of the ion exchanger, while another must migrate from the exchanger into the solution. The rate controlling step was shown by Boyd et al (1947) to be diffusion either in the resin particle itself or in an adherent stagnant films. As particle and film diffusion are sequential steps, the slower of the two is the rate controlling step. The best method for distinguishing experimentally between particle diffusion and film diffusion controls is by interruption test in which the ion-exchange reaction is stopped by removing the resin from the solution of a short period of time. In case of particle diffusion, the concentration gradients in the resin particles will level out and on reimmersion the exchange rate will be higher than at the movement of interruption. With film diffusion, control of rate depends on the concentration differences across the film and these are not affected by the interruption. It has been reported that the release process of ionic drug ions from the resinates eluted with simulated gastric or intestinal fluids is controlled by particle diffusion. Moreover, film diffusion is the rate controlling step in the adsorption of drug ions when present in low concentration and particle diffusion predominates when the adsorbing ions are present in high concentration (Reichenberg 1953) Since the resinate formation in the present study was conducted at reasonable high concentration, the exchange rate should
be controlled by particle diffusion. A mathematical expression for particle diffusion exchange process has been represented by Boyd et al (1947).

Assuming that all resin particles are uniform spheres of radius r, Boyd et al (1947) showed that, under conditions where particle diffusion is the rate controlling step, the fraction of drug release (F) as a function of time is given by:

$$ F = 1 - \sum_{n=1}^{\infty} \frac{6}{\pi^2 n^2} e^{-n^2 Bt} $$

Where $Q_t$ and $Q_\alpha$ are the amount of released at time $t$ and at time $\alpha$, respectively, and $B$ being the effective diffusion coefficient of infinite solution volume, obtained when a solution of constant composition is continuously passed through the thin layer of beads, or in a batch experiment if the solution volume is large.

By Fourier transformation and integration Reichenberg (1953) presented the above expression in the following forms:

$$ Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi(1 - \frac{\pi F}{3})^{1/2} \quad \text{when } F \leq 0.85 $$

$$ Bt = - \log_e \left( \frac{\pi^2}{6} \right) (1 - F) \quad \text{when } F > 0.85 $$

Where, $F =$ fractional adsorption or desorption value at time $t$

$$ B = \text{adsorption or desorption exchange rate constant} $$

$$ B = 4\pi^2 \frac{D}{d_p^2} \quad \text{where } D = \text{diffusion co-efficient of the drug in the resin (m}^2\cdot\text{min}^{-1}) $$

By plotting $Bt$ values vs experimental values of time, a straight line passing through the origin with a slope equal to $B$ should be obtained. From this value of $B$ the effective diffusion coefficient $D$ can be calculated.

A simple procedure has been developed recently by Bhaskar et al (1986) to test the particle diffusion controlled release of drug, which avoids the repeated consultation of Reichenberg equation. The equation suggested by Bhaskar et al (1986) is as follows:
\[- \ln(1-F) = \log \frac{Q_0}{Q} = 1.59 \left( \frac{3}{r} \right) D^{0.65} t^{0.65}\]

This equation suggests that the simple checking of linearity between \(- \ln(1-F)\) and \(t^{0.65}\) is sufficient to establish which is the determining mechanism of liberation process.

When the fractional exchange data of diltiazem was plotted as \(B_t\) vs \(t\), straight lines passing through the origin were obtained (Figure 24). Similarly, \(B_t\) vs \(t\) plots for propranolol were also linear except for the bigger resin particles (Figure 25), in which \(B_t\) vs \(t\) plot was found to consist of two phases. Similar observation has been reported for adsorption of propranolol onto Amberlite IRP-69 (Burke et al 1986). The formation of first phase was due to adsorption of propranolol onto the active sites present on the surface of the resin and this was followed by swelling of the resin and subsequent entry

![Fig. 24.Bt-t plots for adsorption of diltiazem on cation exchange resin having different size and at reflux condition (■). Key – (◆) 100-200 mesh, (▲)240-300 mesh, (●)300-350 mesh.](image)
of the drug ions into the interior of the resin to bind with more active sites. This resulted in the formation of the second phase. These results indicate that adsorption of the drugs onto the resin particles followed particle diffusion process. With a view to further confirm the particle diffusion mechanism, the data were plotted as $\ln \left( \frac{Q_0}{Q} \right)$ vs $t^{0.65}$ following the equation of Bhaskar et al (1986) and the corresponding plots for diltiazem and propranolol are shown respectively in Figures 26 and 27. In both cases, linear relationships were observed confirming the fact that adsorption of drugs followed the particle diffusion process. The adsorption exchange rate constants ($B$) and diffusion coefficients ($D$) of diltiazem were calculated from Boyd’s equation and have been
Fig. 26. – \(-\ln(1-F)\) vs \(t^{0.65}\) plots for adsorption of diltiazem on cation exchange resin having different size and at reflux condition (■). Key – (◆) 100-200 mesh, (▲) 240-300 mesh, (●) 300-350 mesh.

Fig. 27. – \(-\ln(1-F)\) vs \(t^{0.65}\) plots for adsorption of propranolol on cation exchange resin having different size and at reflux condition (■). Key – (◆) 100-200 mesh, (▲) 240-300 mesh, (●) 300-350 mesh.

The results show that decrease in size of the resin increased both the values of B and D. Similarly the values of B and D for propranolol were found to
Table 4
Effect of resin size and loading temperature on adsorption exchange rate constant and diffusion co-efficient of diltiazem.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Size range of resin</th>
<th>Adsorption exchange rate constant (B), h⁻¹</th>
<th>Diffusion coefficient (D), µm²·h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>100°C</td>
<td>100-200 mesh</td>
<td>0.936</td>
<td>294.6</td>
</tr>
<tr>
<td>30°C</td>
<td>240-300 mesh</td>
<td>5.106</td>
<td>435</td>
</tr>
<tr>
<td></td>
<td>300-350 mesh</td>
<td>7.87</td>
<td>468.6</td>
</tr>
<tr>
<td>100°C</td>
<td>100-200 mesh</td>
<td>3.618</td>
<td>1139.35</td>
</tr>
</tbody>
</table>

The release of both the drugs from the resinate also followed particle diffusion process as evident from the linear relationship between Bt vs t (Figure 28 and 29) and between ln Q₀/Q vs t₀.₆⁵ (Figure 30 and 31). The values of B, the desorption exchange rate constants and D, the diffusion coefficients increased as the size of the resinate decreased with decrease in size of the resin (Table 5). Reduction in size of the resins exposed the active sites from the interior of the resin as well as reduced the diffusional path length and resulted in increase in the values of B and D. Moreover, the values of B and D for both the drugs were higher when the equilibrium studies were conducted at higher temperature (100°C). This increase was probably due to more swelling and expansion of the resins at higher temperature giving more access of the drug ions to the exchangeable sites.

Table 5
Effect of resin size and loading temperature on adsorption exchange rate constant and diffusion co-efficient of propranolol.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Size range of resin</th>
<th>Adsorption exchange rate constant (B), h⁻¹</th>
<th>Diffusion coefficient (D), µm²·h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First phase</td>
<td>Second phase</td>
<td>First phase</td>
</tr>
<tr>
<td>100°C</td>
<td>100-200 mesh</td>
<td>1.074</td>
<td>338.22</td>
</tr>
<tr>
<td>30°C</td>
<td>240-300 mesh</td>
<td>1.686</td>
<td>143.67</td>
</tr>
<tr>
<td></td>
<td>300-350 mesh</td>
<td>2.634</td>
<td>156.94</td>
</tr>
<tr>
<td>100°C</td>
<td>100-200 mesh</td>
<td>1.668</td>
<td>525.27</td>
</tr>
</tbody>
</table>
Fig. 28. Bt-t plots for desorption of diltiazem on cation exchange resin having different size and at reflux condition (■) in SIF (pH 7.2). Key – (◆) 100-200 mesh, (○) 240-300 mesh, (▲) 300-350 mesh.

Fig. 29. Bt-t plots for desorption of propranolol on cation exchange resin having different size and at reflux condition (■) in SIF (pH 6.8). Key – (◆) 100-200 mesh, (○) 240-300 mesh, (▲) 300-350 mesh.
Fig. 30. $-\ln (1-F)$ vs $t^{0.65}$ plots for desorption of diltiazem on cation exchange resin having different size and at reflux condition ($\square$) using phosphate buffer (pH 7.2). Key – (◆) 100-200 mesh, (■) 240-300 mesh, (▲) 300-350 mesh.

decreased (Table 6 and 7). Decrease in resin diameter reduces the diffusional path length...
Table 6  
*Effect of resin size and loading temperature on desorption exchange rate constant and diffusion co-efficient of diltiazem in SIF (pH 7.2).*

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Size range of resin</th>
<th>desorption exchange rate constant (B), h⁻¹</th>
<th>Diffusion coefficient (D), µm².h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>100°C</td>
<td>100-200 mesh</td>
<td>0.372</td>
<td>117.15</td>
</tr>
<tr>
<td>300°C</td>
<td>240-300 mesh</td>
<td>0.90</td>
<td>76.69</td>
</tr>
<tr>
<td>100-200 mesh</td>
<td>300-350 mesh</td>
<td>1.542</td>
<td>91.88</td>
</tr>
</tbody>
</table>

and thereby increases the rate of ion-exchange interaction (Irwin et al 1987; Irwin et al 1990). On the other hand, the release of both the drugs from the resinates prepared under reflux condition (100°C) were less and consequently the value of B and D were less than the corresponding values obtained from the resinate prepared at 30°C. As stated earlier that increase in temperature causes expansion of resin particles allowing more access of drug ions to enter into the resin particles and to the deeper exchange sites. However, on cooling, the resin relaxes entrapping ions and thus provides a greater diffusional resistance to elution of drugs (Irwin et al 1990).

The effect of ionic strength on the release of the drugs have been shown in Table 8 and Table 9. Increase in ionic strength enhanced the liberation of drugs from the resinates due to influx of more competitive ions.
Table 8
Desorption exchange rate constant and diffusion coefficient of diltiazem from resinates (100-200 mesh) in pH 3 having different ionic strengths.

<table>
<thead>
<tr>
<th>Ionic strengths (µ)</th>
<th>Desorption exchange rate constant (B), h⁻¹</th>
<th>Diffusion coefficient (D), µm².h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.30</td>
<td>94.47</td>
</tr>
<tr>
<td>0.10</td>
<td>0.426</td>
<td>134.15</td>
</tr>
<tr>
<td>0.15</td>
<td>0.546</td>
<td>171.94</td>
</tr>
</tbody>
</table>

Table 9
Desorption exchange rate constant and diffusion coefficient of propranolol from resinates (100-200 mesh) in pH 3 having different ionic strengths.

<table>
<thead>
<tr>
<th>Ionic Strengths (µ)</th>
<th>Desorption Exchange Rate Constant (B), h⁻¹</th>
<th>Diffusion Coefficient (D), µm² h⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.2513</td>
<td>79.14</td>
</tr>
<tr>
<td>0.30</td>
<td>0.5559</td>
<td>175.06</td>
</tr>
<tr>
<td>0.50</td>
<td>0.6634</td>
<td>208.91</td>
</tr>
</tbody>
</table>

5. Conclusion

The study revealed that reasonably large amount of diltiazem and propranolol can be loaded onto Indion 254(R), a cation exchange resin although the formulation parameters influenced the drug loading to some extent. The resinate having smaller size (240-300 mesh and 300-350 mash) discharged both the drugs quite rapidly and almost independent of pH. Although of both the drugs from the resinates having bigger size (100-200 mesh) apparently appeared to provide prolonged release, about 80% of the loaded drugs were released in 3h for diltiazem and 5.5h for propranolol. Hence there is an opportunity to modify the resinate dosage forms so as to provide further prolongation of drug release in more controlled manner. With this view, the further work was designed to prepare microcapsule dosage form of the resinate having smaller resin size. Polystyrene was selected as a synthetic polymer to coat the resinate through oil in water emulsion solvent evaporation method.