THE EFFECT OF LOADING SOLUTION AND DISSOLUTION MEDIA ON RELEASE OF DICLOFENAC FROM ION EXCHANGE RESINS

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ABSTRACT

Drugs can be loaded on ion exchange resins in order to control their release. Loading of diclofenac sodium on the resin beads not only sustain its release but also reduce its gastrointestinal mucosal injury. In this study the effect of loading solution and concentration of diclofenac in loading solution on total amount of drug loaded on the resin beads (Amberlite IRA-900) and the release characteristic of drug in different media were examined. Results showed that diclofenac resin complex did not release their drug content in simulated gastric fluid but released it in simulated intestinal fluid independent of exposure time in acidic conditions. The effect of a number of parameters such as ionic strength and pH on the release characteriste of drug-resin complexes were also examined. Results showed that although ionic strength is an important factor, drug release is more affected by the pH of the media.

Keywords: Ion exchange resins, Diclofenac sodium, Controlled drug release

INTRODUCTION

A continuous and uniform release of a drug over a long period of time may be obtained if it is chemically bound to a solid carrier, from which it is slowly released by the action of gastrointestinal fluid. Examples of such carriers are ion exchange resins, which have been used for several drugs in order to sustain or control their release (1) or to increase their gastric residence time (2). Ion exchange resins consist of two principal parts: a structural portion consisting of a polymer, mostly styrene crosslinked with divinyl benzene, and a functional portion, which is the ion-active group to which the drug is bounded. Ion exchange resins according to their functional group fall into two broad classifications, cation exchangers and anion exchangers and drugs with the appropriate charge may bind to the functional group of the resin backbone. When this drug-resin complex reaches the gastrointestinal tract, the reverse reaction takes place and the drug is released. Loading and release of drugs from ion exchange resins may depend on many factors such as size and concentration of the ions being exchanged, dissociation constant of the drug, ionic strength and pH of the medium (3,4). Diclofenac sodium is an ideal candidate for formulation in a sustained release form due to its

rapid elimination and its adverse gastrointestinal reaction (5). A number of investigations have been carried out using ion exchange resins as a delivery system for diclofenac (6-9). Some investigators have attempted to suppress drug release in the stomach and its damages to the stomach by using coated ion exchange resin loaded with diclofenac (10). Torres et al. believe that drugs with low acid solubility will precipitate in the acidic medium on release (11). The main aim of this study was to investigate the release characteristics of diclofenac from anion exchange resins in simulated gastrointestinal fluids and to examine if exchange of diclofenac takes place in acidic conditions.

MATERIALS AND METHODS

Drug loading

Resin beads were purified prior to use by successive washing in deionised water, 95% and 50% ethanol and finally deionised water (1). To prepare the diclofenac resin complex, resin beads (600μ, Amberlite IRA-900, Röhm & Hass, France) were treated with either aqueous or hydroalcoholic solution (50%) of diclofenac sodium as follows:
One gram of the purified resin beads was placed in 400 ml of 0.025 M aqueous solution of sodium

diclofenac (Ciba-Geigy, Switzerland) or 200 ml of 0.05 M hydroalcoholic solution of sodium diclofenac and continuously agitated at a rate of 500 rpm for 2 hours followed by washing and drying at room temperature.

The effect of the concentration of loading solution on the total amount of drug loaded on the resin beads was studied using 0.01, 0.02, 0.05, 0.1 M hydroalcoholic solutions of 1.5 mEq sodium diclofenac. In this experiment 1g of resin beads was treated with above solutions for 24 hours followed by washing and drying at room temperature.

Drug content measurement
Measurement of the remaining drug in the effluent and complete release of the drug loaded on the beads was used to determine the total amount of the drug loaded on the resin beads. Remaining drug in the effluent solution was measured spectrophotometrically at 275 nm and 282 nm for aqueous and hydroalcoholic solutions respectively. 0.1 g of drug-resin complex was placed in a beaker containing 900 ml KCl (0.4M) at a constant temperature of 37°C while stirring at 50 rpm. The medium was replaced every 24h with fresh solution. The amount of diclofenac in solution was determined using UV spectroscopy at 265 nm. The process was continued until the UV absorbance of the solution remained constant. The difference between the weights of the resin beads before and after drug loading was also used as a parameter to determine the total amount of the drug on the drug resin complexes

Drug release
Drug release from drug-resin complexes was studied using the USP method II dissolution apparatus. Drug resin complex (0.1 g) was placed in a dissolution vessel containing 900 ml of either simulated gastric fluid without enzyme (pH 1.09) or simulated intestinal fluid (pH 6.8) or KCl (0.4M, pH 5.2) according to Raghunathan studies (12).

The solutions were prepared freshly. The temperature was kept at 37°C and vessels were covered to prevent evaporation during the experiment

The medium was stirred with a two-bladed paddle at 50 rpm. At appropriate intervals, 5 ml of the medium were taken and the amount of drug released was measured at 273 nm for simulated gastric fluid, 276 nm for simulated intestinal fluid and 265 nm for KCl.

To investigate the probable amount of drug released and precipitated in simulated gastric fluid, the USP open flow through cell (apparatus IV) was applied. 0.1g of drug-resin complex was placed in a small dissolution cells kept at 37°C. 2.5 litre of simulated gastric fluid with flow rate of 7 ml/min was passed through each cell. The continuous flow of the medium not only achieves sink condition but also allows precipitated drug particles to leave the cells. Fluid exiting from the cells was mixed with the same volume of NaOH (0.2M) to adjust the pH at 12 and the absorbance of the samples was measured for diclofenac at 275 nm. Each experiment was repeated 6 times. The influence of exposure time in simulated gastric fluid on the subsequent release in simulated intestinal fluid was investigated. 100 mg resin beads were placed in contact with simulated gastric fluid for 30, 60, 120, 180, 240 and 360 min before being transferred to simulated intestinal fluid. Drug release in this medium was studied as detailed above.

RESULTS AND DISCUSSION
To endeavour to increase the drug content of the resin beads, sodium diclofenac was added in water and hydroalcoholic solution was added to a fixed amount of resin beads. Alcohol was added to the loading solution to increase solubility of the drug in aqueous solution. The mean amount of drug loaded on 1 g resins was 672±19.7 mg and 604.4±21.46 mg from aqueous and alcoholic loading solution respectively. The mean bead size measured by standard sieve method after drug loading was 703μ and 625μ with aqueous and alcoholic solution respectively. Despite the increase in solubility, the alcoholic solution did not increase the capacity of the resin beads for diclofenac and even caused a reduction in drug loading. Some free drug molecules will be loosely attached to the surface of the beads after preparation and these will be easily removed during the washing process. This drug loss is increased when the hydroalcoholic solution is used. In addition, by increasing the amount of alcohol in the solution, the acid dissociation constant of sodium diclofenac and as result proportion of ionised diclofenac is decreased (13) and consequently the loading capacity of the resin for diclofenac is being lowered (theoretical capacity

of this resin according to manufacturer for HCl is 4.2). The total amount of the drug eluted from 1 g of drug-resin complex by using KCl solution as eluents were 469.4 mg and 427.7 mg for aqueous and hydroalcoholic solution respectively. These amounts are similar to the amount loaded on 1g resin as it was determined by spectrophotometric measurement of the eluted solution. These results show that the total amount of diclofenac loaded on the resin beads could be available for *in vivo* absorption. The effect of concentration of loading solution on the total capacity of the resin beads for diclofenac was also studied. Results also showed that in the applied range, changing the concentration of loading solution has no effect on total drug loading (Table 1).

From these results the equilibrium constant between diclofenac and chloride ions (K_{Cl}^{D}) can be calculated by applying equations I and II.

Equation I

$$K_{Cl}^{D} = \frac{[D]_r [Cl^-]_s}{[D]_s [Cl^-]_r} = \frac{\dfrac{(m_D)_r}{V_r} \cdot \dfrac{(m_{Cl})_s}{V_s}}{\dfrac{(m_D)_s}{V_s} \cdot \dfrac{(m_{Cl})_r}{V_r}}$$

$$K_{Cl}^{D} = \frac{(m_D)_r (m_{Cl})_s}{(m_D)_s (m_{Cl})_r}$$

Equation II

Where $[D]_s$, $[D]_r$ are drug concentrations in mEq/ml in the solution and inside of the resin. $[Cl]_s$, $[Cl]_r$ are chloride ions concentration in the solution and resin. V_s and V_r are volume of solution and resin beads in ml. (m_D) and (m_{Cl}) are amounts of diclofenac and Cl ions. Based on these calculations, the equilibrium constant is a function of the amount of ions rather than its concentration. This finding is in agreement with the results obtained from the experimental studies. As the volume of solutions containing resin beads and loading solution is constant, K_{Cl}^{D} can be calculated on the basis of the amount of ions in both phases. Table 1 shows the calculated equilibrium constant of 1.5 mEq/g sodium diclofenac in loading solution. The mean amount of drug loaded on the drug resin complexes was 0.89±0.068 mEq/g and K_{Cl}^{D} is

0.43±0.126. The mean amount of drug loaded on the drug resin complexes that have been in contact with excess of sodium diclofenac (10mEq/g) in alcoholic solution is 2.33 mEq. The equilibrium constant obtained from this experiment is 0.423, which is not much different from that obtained from different concentration and amounts of drug in loading solution.

The amount of the drug loaded on the resin is less than the capacity of the resin. It can be concluded firstly that the amount of the ions in the loading solution affects the total amount of drug on the resin and secondly, in a batch operation, the complete capacity of the resin cannot be obtained.

Table 1. Total amount of drug loaded on drug resin complexes and equilibrium constant of loading reaction for different concentrations 1.5 mEq/g of diclofenac in loading solution

Concentration (M)	Drug loaded		Equilibrium constant
	mg/g	mEq/g	
0.01	219.9	0.85	0.35
0.02	252.2	0.97	0.60
0.05	238.2	0.92	0.47
0.10	213.3	0.82	0.31
Mean	230.9	0.89	0.43
SD	17.68	0.068	0.126

Table 2. Total drug released from drug resin complexes in simulated intestinal fluid being in contact to acid for different periods of time

Exposure time to acid (min)	Drug Released (%±SD)
0	15.8±0.28
30	15.5±0.3
60	15.2±0.25
120	15.9±0.21
180	15.7±0.32
240	15.3±0.19
360	15.4±0.20
Mean	15.5±0.22

Drug release

Drug release from ion exchange resins loaded with diclofenac was studied in simulated gastric fluid. Because a spectrophotometric method was used, no drug was detected in the medium, as it was expected from the results of Torres et al. (11). These authors have stated that the precipitation of the sodium diclofenac in gastric fluid is the main

factor for the lack of drug release in this medium. In fact they concluded that the drug is released after exchange with existing ions and because of the low solubility of diclofenac in acidic solution and the its precipitation, it is not detectable. In this study it is shown that release of the drug from drug resin complex does not occur. To further study this, the open dissolution method was applied. The pH of the collected medium was adjusted to alkaline by means of sodium hydroxide (0.2 M) in order to dissolve any precipitated diclofenac in the simulated gastric fluid. After changing the pH, the amount of the drug in the solution was assayed spectrophotometrically. The results are shown in Figure 1 and indicate that, even allowing for precipitated drug, the release in acidic medium was negligible (3.8%). To confirm this, drug resin complex was placed in simulated gastric fluid at different periods of time and the content of drug remaining in the beads was investigated in simulated intestinal fluid. The results, given in Table 2, show that the amount released in simulated intestinal fluid is independent of the time of pretreatment in acidic conditions (P<0.4). Ming-Jhau et al. claimed that in spite of the absence of drug release in the simulated gastric fluid, the length of the time that a preparation (an enteric-coated tablet containing diclofenac) is retained in simulated gastric fluid affected the rate and extent of drug release after transformation to the simulated intestinal fluid (14). They believed that this might be caused by the deposition of a layer of insoluble drug around the preparation. This was not the case with the drug resin complex. As shown in figure 2, the period of exposure time to simulated gastric fluid did not even change the profile of drug release in simulated intestinal fluid. Therefore one can conclude that ion exchange between ions in the acid medium and diclofenac on the resin beads has not occurred. Precipitation of the released diclofenac on the surface of the resin beads is not also the reason for the absence of diclofenac in simulated gastric fluid. Therefore, diclofenac can be protected from release in the stomach by loading on the ion exchange resins. Figure 1 compares drug release profiles from drug resin complexes in KCl medium (0.4N, pH 5.2) and simulated intestinal fluid. Drug release from resin beads in KCl was fast and complete in comparison with the pattern of drug release in simulated intestinal fluid. As can be seen, the elution half-life ($t_{50\%}$) in KCl was 180 min and

80% of the drug was released in 600 min. One explanation for this observation is the ionic strength differences between the media. One of the factors that affect drug release from ion exchange complex is ionic strength, since increasing the ionic strength of the medium facilitates ion exchange (4,15). Ionic strength of the KCl solution is higher (μ=0.4) in comparison with that of the simulated gastric fluid (μ=0.1185). However more drugs are released in simulated intestinal fluid, which has an ionic strength (μ=0.079) less than that of the simulated gastric fluid. Therefore one can conclude that the ionic strength is not the main factor in controlling drug release from drug resin complexes but the pH of the medium could be the more important factor to be considered.

To study the actual effect of the ionic strength of the medium, drug release was investigated in KCl. In this study pH of the medium was kept constant at 5.2 while ionic strength was varied (0.2, 0.3, 0.4). Diclofenac release in KCl (pH 5.2) changed by ionic strength of the medium and increasing the ionic strength increased drug release (Fig. 3). Rate of drug release in KCl (μ 0.4) at pH 1.1 was negligible (2% after 8 hours). The effect of the pH on drug release in KCl (0.4N) was investigated in media with constant ionic strength (μ=0.4) and different pHs (1.1, 5.2 and 6.8). Increasing pH to 5.2 while keeping ionic strength constant caused faster drug release. However changing pH of the medium toward the more neutral (pH 6.8) did not increase the drug release from DRC (fig. 4). In fact reduction in drug release by reduction of pH at a constant ionic strength follows solubility of the diclofenac in those media. Solubility of diclofenac is 1mg/ml in HCl (pH 1.1), 6mg/ml in phosphate buffer (pH 7.2) and 9 mg/ml in fresh distilled water (pH 5.2).

CONCLUSION

These studies have shown that the amount of the drug released from ion exchange resins loaded with diclofenac in simulated gastric fluid is negligible and suggest that diclofenac can be protected from release in the stomach by loading on to ion exchange resins. Drug release in simulated intestinal fluid from drug resin complexes with and without any exposure to acidic medium was not significantly different (P>0.4) which shows that there is no relation between profile of the drug release and its presence in acidic media.

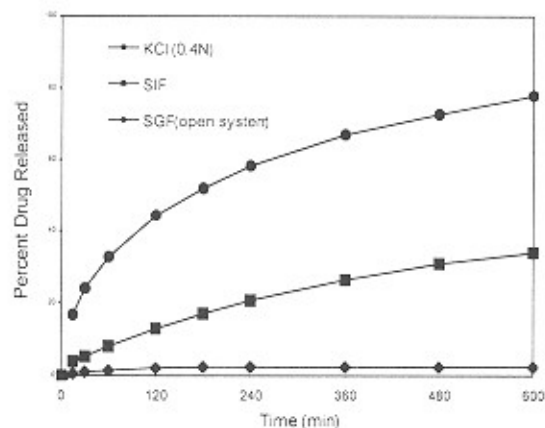**Figure 1.** Drug release from ion exchange resin complexes in KCl, simulated intestinal fluid (SIF) and simulated gastric fluid (SGF), (Mean ±SD).
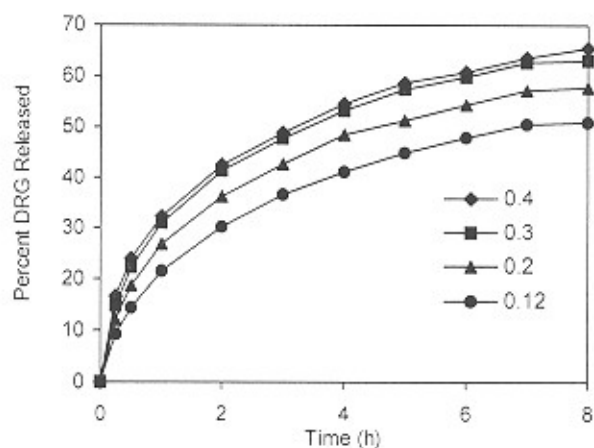

Figure 3. Effect of ionic strength (μ) on drug release from drug-resin complexes in KCl with pH of 5.2 and different ionic strengths.
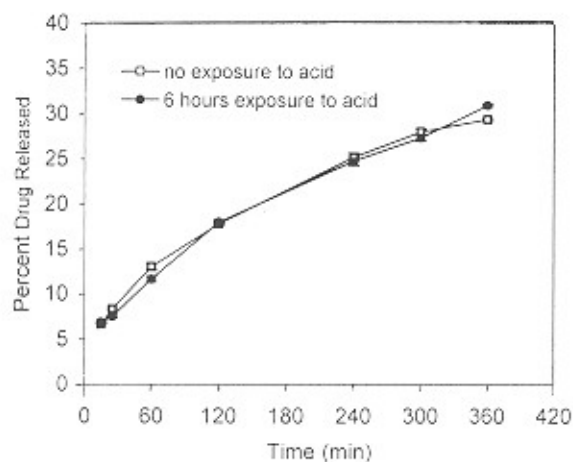

Figure 2. Effect of exposure of the drug resin complexes to the simulated gastric fluid on drug release from drug resin complexes in simulated intestinal fluid (Mean ±SD).
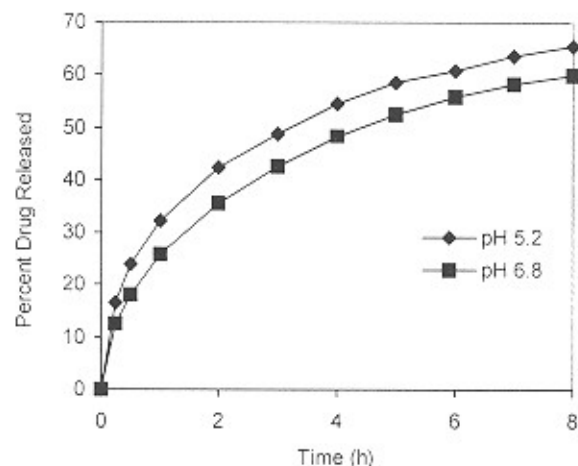

Figure 4. Effect of pH of the dissolution medium on drug release from drug-resin complexes in KCl (0.4N) with ionic strength equal to 0.4μ.

Therefore this system has the capability to be used as a controlled system for diclofenac not only for sustaining its release but also protecting the gastric mucosa from damage. Results showed that the drug release in phosphate buffer (pH 6.8) is facilitated by increasing the ionic strength of the medium.

As it can be seen, the drug release from DRC is related to ionic strength. Although pH plays more important role in constant ionic strength and drug release increases by increasing the pH, solubility of diclofenac in the medium also must be considered.

Further experiments are required to be carried out in order to determine the main factors influencing the release of drugs into media in which they are relatively insoluble.

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