Drug Release Properties of Polyethylene-Glycol-treated Ciprofloxacin-Indion 234 Complexes

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Sambhaji Pisal,[1] Rana Zainnuddin,[1] Pradeep Nalawade,[1] Kakasaheb Mahadik,[1] Shivajirao Kadam[1]

[1]Poona College of Pharmacy and Research Center, Bharati Vidyapeeth Deemed University, Pune - 411 038, Maharashtra, India

ABSTRACT

The polyethylene glycol (PEG) treatment of ciprofloxacin-Indion 234 complex was aimed to retard rapid ion exchange drug release at gastric pH. Ciprofloxacin loading on Indion 234 was performed in a batch process, and the amount of K^+ in Indion 234 displaced by drug with time was studied as equilibrium constant K_{DM}. Drug-resin complex (DRC) was treated with aqueous PEG solution (0.5%-2% wt/vol) of different molecular weights (MWs) for 2 to 30 minutes. The PEG-treated ciprofloxacin-Indion 234 complex was evaluated for particle size, water absorption time, and drug release at gastric pH. During drug loading on Indion 234, the equilibrium constant (K_{DM}) increased rapidly up to 20 minutes with efficient drug loading. Increased time of immersion of the drug resinate in PEG solutions significantly retained higher size particles upon dehydration. The larger DRC particles showed longer water absorption times owing to compromised hydrating power. The untreated DRC showed insignificant drug release in deionized water; while at gastric pH, ciprofloxacin release was complete in 90 minutes. A trend of increased residual particle size, proportionate increase in water absorption time, and hence the retardation of release with time of immersion was evident in PEG-treated DRC. The time of immersion of DRC in PEG solution had predominant release retardant effect, while the effect of molecular weight of PEG was insignificant. Thus, PEG treatment of DRC successfully retards ciprofloxacin ion exchange release in acidic pH.

Keywords: ciprofloxacin, Indion complexes, PEG immersion, particle size, water uptake, release

INTRODUCTION

A substantial amount of research has been published concerning pharmaceutical utility of ion exchange resins for sustained release, targeted drug delivery, and taste protection.[1,2] Factors that control the release rate of drug are particle size of resin, degree of cross-linking, and chemistry of resin and complex.[3-5] The drug resin complexes of phenylpropanolamine with amberlite IR NO120 (or XE69) for sustained release required coating with ethyl cellulose solution by spray-drying technique.[6] Cuna et al[7] aimed to prepare terbutaline-dowex 50W complex for controlled-release suspensions. The difficulty was encountered in drug diffusion in suspending vehicle-producing release in acidic environment. Microencapsulation of drug-resin complex with Eudragit RS (or RL) through emulsion-solvent evaporation technique provided the desired protection. Betty et al have patented a mixture of coated and noncoated sulfonic acid resins loaded with dextromethorphan for taste masking and sustained release.[8] Similarly, coating of pseudoephedrine-dowex 50 WX8 complexes with carnauba wax for sustained release has been reported by Patricia et al.[9] The coated drug resin complex particles showed fracturing of the coat, necessitating impregnation, thus complicating the process feasibility.

Although drug release can be retarded by forming drug-resin complexes, the need to further retard release of ciprofloxacin has been demonstrated.[10-11] Considering the limited feasibility of reported methods, complexation of ciprofloxacin with Indion 234 and subsequent PEG solution treatment, to obtain retarded stomach release has been exploited. Indion 234 is an inexpensive, water insoluble, high molecular weight polycarboxylic acid amorphous resin.[12] The weak cation exchange resin has $–COO^–K^+$ functional group attached to cross-linked polystyrene backbone. The highly porous indigenous resin swells extensively (500 times) by hydration in aqueous systems. Indion 234 is commonly used as superdisintegrant in tablets. Ciprofloxacin has requisite aqueous solubility (pK_a 6-8) and complexation ability. PEGs are used in concentration in excess of 20% wt/vol as impregnating agents for drug-resin complexes to improve the subsequent coatability with water-insoluble polymers.[13] The drug release at gastric pH from drug-resin complex can be retarded by treating the complexes with dilute PEG solutions. The effect of PEG treatment on particle size and water absorption rate of drug-resin complex is investigated to support the hypothesis.

Corresponding Author: Sambhaji Pisal, Poona College of Pharmacy and Research Center, Bharati Vidyapeeth Deemed University, Pune - 411 038, Maharashtra, India. Tel: +91-020-25437237. Fax: +91-020-25439383. E-mail: sspisal@rediffmail.com.

Materials and Methods

Materials

Ciprofloxacin hydrochloride (batch no. 007742001) was a gift sample from Get-Rid Pharmaceuticals, Pune, India. The resin, Indion 234, was procured from Ion Exchange India Ltd., Mumbai, India. PEGs (molecular weight [MW] 4000, 6000, and 15 000) were purchased from E. Merck India Ltd, Mumbai, India. Deionized water was obtained using NANOpure Diamond water purification system (Barnstead Thermolynr, Dubuque, IA).

Methods

Formation of Ciprofloxacin-Indion 234 Complex

The particle size, loading capacity, and water-absorption time of Indion 234 was determined. In a batch process, 500 mg of activated resin was placed in a beaker containing 25 mL of deionized water and allowed to swell for 30 minutes.[14] Five hundred milligrams of ciprofloxacin (as per 1:1.3 drug: resin [D:R]) was accurately weighed, added, and stirred for 5, 10, 15, 20, 30, and 240 minutes. The amount of K^+ in Indion 234 displaced by drug (loading efficiency) was calculated by spectrophotometric (274 nm) analysis of unbound fraction in solution. The equilibrium constant K_{DM} was calculated using Equation 1.

$$K_{DM} = \frac{[D]r \times [M]s}{[D]s \times [M]r}, \qquad (1)$$

where *[D]r*, *[M]r*, *[D]s*, and *[M]s* are drug and metal concentration in resin and solution, respectively.

Polyethylene Glycol Treatment of Drug-Resin Complex

PEG 4000, 6000, and 15 000 aqueous solutions each of 0.5%, 1%, and 2% wt/vol were prepared separately. One milliliter of PEG solution was added slowly to 500 mg of DRC, placed in a watch glass, and treated for 2, 10, and 30 minutes, respectively. Each mixture was filtered at the respective time, and the complex was vacuum dried (40°C) to constant weight. The PEG-treated DRCs were evaluated further.

Analysis of Drug-Resin Complex

The particle sizes of plain resin, DRC, and various PEG-treated complexes were measured using optical microscopy and analyzed using Bivimplus software (ExpertVision, Mumbai, India). The powder particles were placed on a glass side and an average particle diameter for 300 particles was recorded. The surface topography of untreated and PEG-treated DRC was observed using a scanning electron microscope (SEM, Cambridge Instruments, Stereoscan S120, Cambridge, UK). The particles were gold coated (20 nm) using sputtering technique (E5200 automatic, Sputter Coater, Bio-Rad, Oxford, UK) and photographed (original magnification, × 50).

Water Absorption Study

Five hundred milligrams of accurately weighed Indion 234, DRC, and PEG-treated DRCs were placed separately in Petri dishes. A measured amount of deionized water (1 mL) was added slowly into the Petri dish. The time required for the complete water absorption was measured in triplicate.[15] The batch size was maintained constant, and the water absorption analysis of each PEG-treated DRC was performed in triplicate.

Drug Release From Drug-Resin Complexes

Drug release from plain DRC (1:1.3) in deionized water (900 mL, 37°C, 100 rpm), and at pH 1.2 using 900 mL of 0.1 N HCl for 120 minutes, was determined using a *United States Pharmacopeia (USP)* 24 type-II dissolution apparatus. Similarly, drug release from PEG-treated DRC, equivalent to 500 mg of ciprofloxacin hydrochloride was performed. Two milliliters of each sample was removed at 15, 30, 60, 90, and 120 minutes. The filtrate was assayed for free drug. The spectrophotometric estimation of ciprofloxacin in deionized water at 274 nm was performed with the standard curve of *a* (slope) = 11.153, *b* (constant) = –0.055 and *R* (coefficient of correlation) = 0.9994, and in 0.1 N HCl at 278 nm with *a* = 10.708, *b* = –0.108, and *R* = 0.9994, respectively. The values of slope, constant, and *R* in both the curves indicate linearity of UV absorbance with drug concentration.

Results and Discussion

Complexation Process

Ciprofloxacin-Indion 234 complexation for bitterness masking and improved palatability for patients was investigated in our laboratory. Complexation with ion exchange resin is an efficient technique that can be easily adaptable to industrial scale. The drug being soluble in water has the desired ionization power. The size of Indion 234 particles obtained, 54 ± 4 μm, was in conformation with the reported size (<150 μm), which is useful for complexation in batch process. (Substantially small size particles are difficult to process and particles greater than 200 μm have a tendency to fracture.) The water uptake time of Indion 234 was found to be 45 ± 2 seconds. Indion 234 is highly porous and, even though insoluble in water, is capable of hydration. The loading capacity of Indion 234 is a function of exchange of K+ ions in the

Table 1. Equilibrium Constant of Ciprofloxacin Loading on Indion 234 With Time*

Time in Minutes	[D]r	[M]s	[D]s	[M]r	Equilibrium Constant (K_D^M)
5	1.50×10^{-4}	1.40×10^{-4}	12×10^{-4}	26.0×10^{-4}	0.49
10	1.70×10^{-4}	1.30×10^{-4}	14×10^{-4}	25.0×10^{-4}	0.73
15	3.17×10^{-4}	1.10×10^{-4}	17×10^{-4}	22.5×10^{-4}	1.49
20	4.80×10^{-4}	0.85×10^{-4}	19×10^{-4}	19.5×10^{-4}	3.20
30	5.10×10^{-4}	0.502×10^{-4}	22×10^{-4}	17.9×10^{-4}	7.34
240	5.09×10^{-4}	0.499×10^{-4}	21×10^{-4}	17.3×10^{-4}	7.38

*[D]r, [M]r, [D]s, and [M]s indicate drug and metal concentration in resin and solution, respectively.

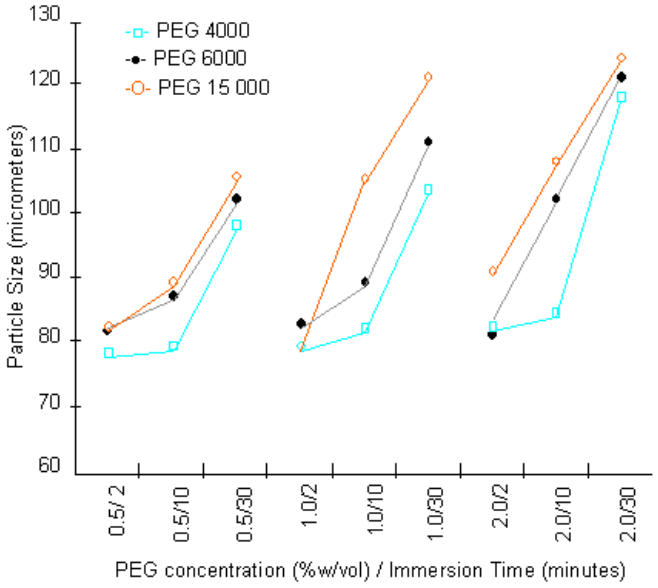

Figure 1. Effect of PEG concentration and treatment time on particle size of DRCs.

resin with the counterions in solution. The loading capacity of 10.4 meq/g was confirmed.

The drug-loading efficiency for a drug-resin ratio 1:1.3 of the batch process was 96.50% ± 1.10%. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution.[16] The unswollen Indion 234, swelling of resin for 10, 20, 30, and 240 minutes produced the drug loading of 77.50% ± 0.82%, 82.03% ± 0.55%, 88.28% ± 0.53%, 96.36% ± 0.17%, and 96.40% ± 0.21% wt/wt, respectively. The results reveal that a 30-minute swelling time of Indion 234 in deionized water gave the maximum ciprofloxacin loading of 96.36% wt/wt. Indion 234 is a high molecular weight, water-insoluble polycarboxylic acid amorphous resin. In unswollen resin matrix, the exchangeable $–COO^-K^+$ functional groups attached to cross-linked polystyrene backbone are latent and coiled toward the backbone, therefore less drug-loading efficiency.[17-18] Equilibrium study results reveal that as time increased, the K_{DM} values increased rapidly up to 20 minutes (Table 1). Although the K^+ release is not much seen after 20 minutes, it is surprising to note the high exchange rate from 20 to 30 minutes. The batch process of drug loading with continuous stirring does not allow the development of a diffusion barrier layer around the resin particle. Hence, the drug diffusion toward $–COO^-K^+$ of resin is rapid. Increasing the complexation time above 30 minutes did not further increase the K_{DM} values. Hence, the 30-minute contact time between drug and resin could be optimized to equilibrate the ion exchange process to achieve maximum drug loading.

Particle Size and Water Absorption Rate of Drug-Resin Complexation

The size of untreated DRC, vacuum dried to constant weight, was 55 ± 3 µm. The effect of PEGs treatment, namely, MW 4000, 6000, and 15 000, in various concentrations (0.5%, 1%, and 2% wt/vol) and time of immersion of DRCs in aqueous PEG solutions on particle size is shown in Figure 1. The particle-size analysis reveals that the increased time of immersion of DRC in PEG solutions significantly increases the size retained by DRC upon dehydration. The proportionate increase was not observed, but as the time of immersion increased from 2 to 10 minutes, 1.2- to 1.5-fold larger size particles were retained. A further increase in PEG treatment time to 30 minutes, shows an average increase of only 16.23% ± 1.22% in DRC size. The identical trend with the time of immersion was observed with the 3 PEG (MW 4000, 6000, and 15 000) concentrations. The concentration of PEG solutions has shown only a slight increase in residual size of DRC within and with increase in molecular weight.

The water uptake times of Indion 234 and untreated DRC were found to be 45 ± 2 seconds and 78 seconds, respectively. The effect of PEG treatment on water absorption time of DRC is shown in Figure 2. A trend similar to the effect on particle size was observed. A 2-, 10-, and 30-minute immersion of DRC in PEG solution (with 3 different MW PEGs and different concentrations) needed an average of 82 ± 8 seconds, 1224 ± 42 seconds, and 1441 ± 57 seconds for complete water absorption, respectively. The water absorption time for PEG 15 000 solution-treated DRC was higher

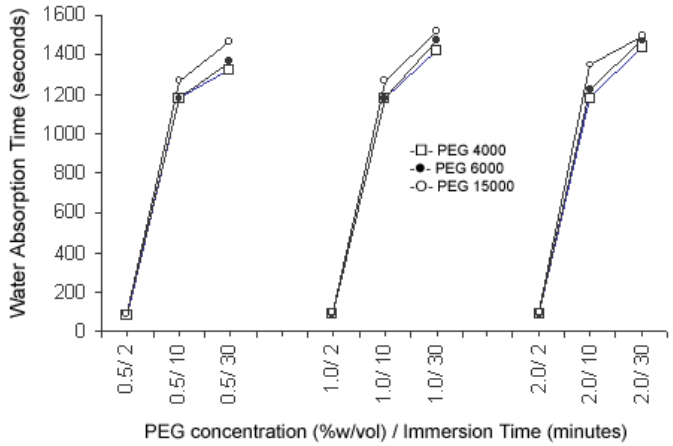

Figure 2. Effect of PEG concentration and treatment time on water absorption time of DRCs.

by 7% ± 0.33% as compared with the other PEGs. The study revealed that as the time of immersion (ie, the particle size) increases, the time for total water absorption increases with a rapid 13-fold increase for 10 minutes of immersion. Although concentration of PEG solution has shown insignificant effect, the solution of higher molecular weight PEG showed a decrease in the water absorption rate of DRC.

Indion 234 is a highly porous, carboxylic acid, weak cationic resin. The resin hydrates by water uptake and swells to produce larger particle size. The resin particles shrink in size upon drying. The higher residual size of treated DRC is due to the penetration of dilute PEG solution through the porous swollen matrix of the DRC. The subsequent dehydration causes the entrapment of the PEG inside the DRC matrix. SEMs of untreated DRC and DRC treated with PEG 15 000 (2% wt/vol, 30-minute immersion of DRC) are shown in Figures 3A and B, respectively. The untreated DRC particle has a smaller size and porous surface. The PEG-treated DRC shows significant particle size enlargement with surface filled to produce a smooth texture. The excess PEG is occasionally deposited on the surface of DRC. However significant amount of PEG is entrapped in the DRC matrix. Deposition of PEG only on the surface of dried DRC and aggregation is ruled out. In such instances, the water uptake time should have been shortened, as PEG is extensively reported for solid dispersions and increasing dissolution rate. Thus the PEG-treated DRCs exhibit larger particle size depending on time of immersion. The larger size particles show significantly longer water absorption times owing to compromised hydrating and swelling ability. The effect of the increase in MW of PEGs on water absorption time is evident; the higher the MW, the longer are the times of water absorption.

PEG, polypropylene glycol, and mannitol are commonly used impregnating agents used for improving coatability of DRCs with water-insoluble polymers.[19] PEGs are used as impregnating agents in concentrations above 25% wt/vol. However, in ciprofloxacin-Indion 234 complexes, PEG treatment was

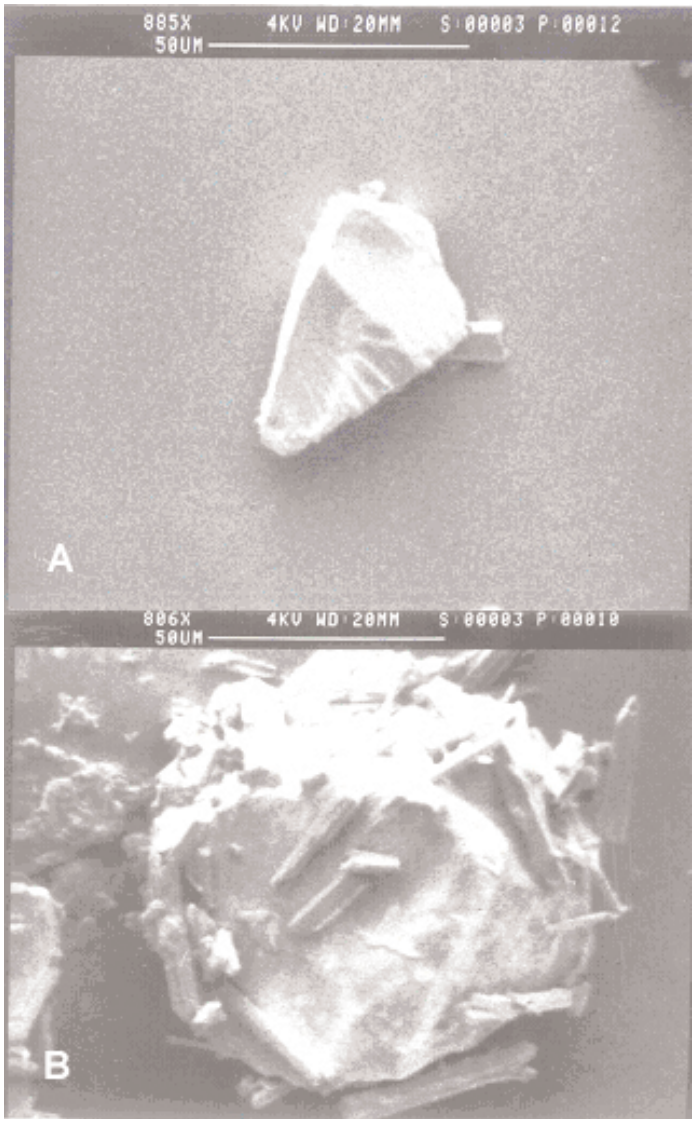

Figure 3. SEMs of DRC: (A) untreated DRC, (B) PEG-treated DRC.

preferred at very low (0.5%-2% wt/vol) strength. Although all grades of PEG are soluble in water, aqueous solutions of higher MW grades (PEG 15 000) show increasing gelling tendency.[20] The higher viscosity may decrease the water penetration in DRC. Water uptake time is indicative of the rate of water penetration into the DRCs. The phenomenon is likely to affect the ion exchange equilibrium drug release process.

Drug Release From Polyethylene Glycol-treated Complexes

Insignificant amount of drug (less than 0.2%) was released in deionized water in 120 minutes, indicating the stability of complexes. At gastric pH (1.2 pH), 59% ciprofloxacin was released in deionized water from DRC within 15 minutes, and the release was complete in 90 minutes. The effect of PEG treatment, namely, PEG 4000, PEG 6000, and PEG 15 000, on drug release in acidic pH from DRC is shown in Figure 4A, B, and C, respectively. The comparison of

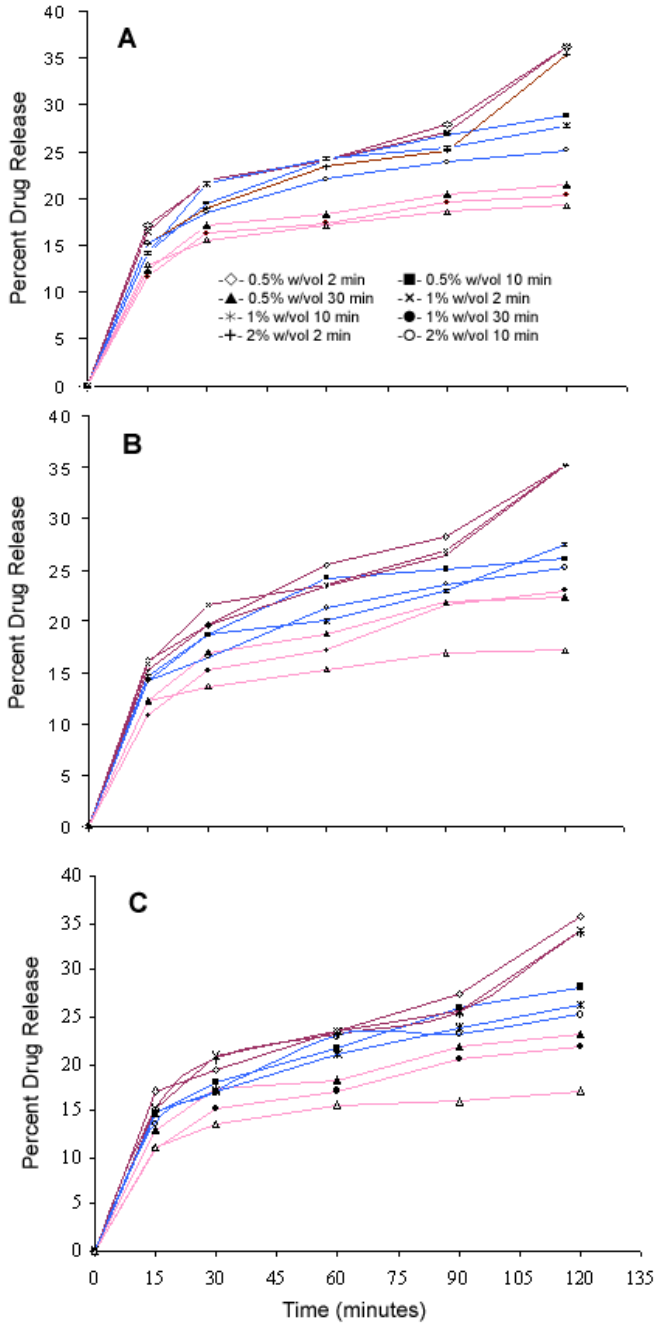

Figure 4. Drug release from DRCs: (A) PEG 4000, (B) PEG 6000, and (C) PEG 15 000.

release profile revealed that PEG treatment significantly retarded the drug release irrespective of the PEG and concentration used. The significant release-retardant effect with the time of immersion of DRC complex was observed with all batches. A trend revealing the effect of concentration was also seen. The amounts released in 120 minutes with PEG 4000, 6000, and 15 000 were found to be in the range of 17% to 35%. The immersion time of 2, 10, and 30 minutes of DRC showed 35.24% ± 1.02%, 26.56% ± 1.85%, and 20.26% ± 1.22% of drug release, respectively. The sustained-release effect was observed with increased time of immersion, and hence from larger size DRCs. This trend in release pattern was uniform in all PEG 4000, 6000, and 15 000 treatments. The release retardant effect of 2-minute immersion of DRC with the 3 MW PEGs begins disappearing at 90 minutes. The inefficient penetration time produced smaller particles with shorter water-absorption time and, hence, showed faster onset of release after 90 minutes.

Particle diffusion and film diffusion are sequential steps in drug release by ion exchange process.[21] The hypothesis is that the equilibrium exchange drug-release process, similar to drug loading, is highly dependent on the physiological pH. The exchange process of drug release follows Equation 2.

$$\text{Resin}^- - \text{Drug}^+ + X^+ \rightarrow \text{Resin}^- - X^+ + \text{Drug}^+, \qquad (2)$$

where X^+ represents the ions in the gastrointestinal (GI) tract.

Indion 234-ciprofloxacin complex hydrates by water absorption and swells in diffusion media; the subsequent exchange process releases the drug. There was no drug release in plain deionized water because ciprofloxacin hydrochloride was completely ionized and therefore bound to the resin. When DRC is exposed to a low pH, it causes dissociation of the complex. The presence of H^+ ions in the medium causes displacement of ciprofloxacin, thus facilitating drug release. Since the water uptake times were increased with PEG treatment, more time was required for ionic exchange between the drug and H^+ ions in the dissolution medium. Consequently, it took more time for the drug to diffuse out of the resin. This, in turn, retarded the drug release from the resonates. The trend of increased residual particle size, proportionate increase in water absorption time, and hence the retardation of release with time of PEG treatment was evident. The ion exchange equilibrium drug-release rate, once retarded in stomach, is expected to proceed slowly in intestinal pH. The stoichiometric ion exchange process is highly dependent on pH and can be used for sustained release of ciprofloxacin.

Conclusion

The rapid ionic equilibrium drug exchange at gastric pH from DRC can be retarded by treating the complexes with dilute PEG solutions (≤2% wt/vol). The trend of increased residual particle size, proportionate increase in water absorption time, and hence retardation of release with time of PEG immersion is evident. Thus, the drug release from ion exchange resin is retarded at gastric pH. The drug-release retardant effect of PEG treatment is interesting considering properties of Indion 234 and the uses of PEG in formulations.

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