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Molecular Properties of Ciprofloxacin-Indion 234 Complexes

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ABSTRACT

The purpose of this research was to formulate tasteless complexes of ciprofloxacin with Indion 234 and to evaluate molecular properties of drug complexes. The effect of batch and column process, complexation time, temperature, and pH on ciprofloxacin loading on Indion 234 is reported. Drug resin complexes (DRC) were characterized by infrared spectroscopy, thermal analysis, and x-ray diffraction pattern. Ciprofloxacin release from DRC is obtained at salivary and gastric pH and in the presence of electrolytes. The efficient drug loading was evident in batch process using activated Indion 234 with a drug-resin ratio of 1:1.3. Drug complexation enhanced with pH from 1.2 to 6, while temperature did not affect the complexation process. Infrared spectroscopy revealed complexation of –NH (drug) with Indion 234. DRC are amorphous in nature. Drug release from DRC in salivary pH was insufficient to impart bitter taste. Volunteers rated the complex as tasteless and agreeable. Complete drug release was observed at gastric pH in 2 hours. The drug release was accelerated in the presence of electrolytes. Indion 234 is inexpensive, and the simple technique is effective for bitterness masking of ciprofloxacin.

KEYWORDS: ciprofloxacin, Indion 234, tasteless complex, characterization, electrolyte, release

INTRODUCTION

Recently, a number of novel techniques for bitterness inhibition in pediatric and geriatric formulations have been attempted. Syrups of cinnamon, orange, cherry, and raspberry can be used to mask salty and bitter tastes. However, the extent of masking is unpredictable because of complex interactions of flavor elements.[1] Bitterness-free vitamin B oral solutions can be prepared by adding sugars, amino acids, and fruit flavors. The bitterness of zinc stearate in lozenges intended for the common cold can be masked with saccharin, anethole-β-cyclodextrin complex, and magnesium stearate. Aspartame, in 0.8% wt/vol has prominence in providing bitterness reduction for 25% acetaminophen granules.[2] Increasing viscosity with rheological modifiers such as gums can lower the diffusion of bitter substance from saliva to the taste buds. Acetaminophen suspensions are similarly formulated with xanthum gum (0.1%-0.2%) and microcrystalline cellulose (0.6%-1%).[3] The mentioned techniques used alone are inefficient to mask the taste of certain drugs, necessitating the use of technological advancements. A taste-masking carrier for acetaminophen comprising melting with stearyl stearate (75°C) and spraying the melt into a fluidized bed has been reported for chewable tablets.[4] Similarly, gabapentin, an experimental drug for seizures, has improved taste when coated with gelatin followed by partially dehydrogenated soybean oil and glycerol monostearate.[4] Kao Corporation (Tokyo, Japan) has reported a homogenized suspension of phosphatidic acid and β-lactoglobulin from soybean and milk to completely suppress the bitter stimulants such as quinine, caffeine, isoleucine, and papaverine hydrochloride.[5] Palatable ibuprofen solutions are prepared by forming a 1:1 to 1:1.5 inclusion complex with ibuprofen and hydroxypropyl-β-cyclodextrin. Such complexation removes the bitterness but creates a sour taste.[6] Chemical modification of drugs for reducing aqueous solubility and hence the taste has proved successful.[7] Coating small drug particles with water-insoluble polymer avoids contact with taste buds and eliminates the objectionable taste. However, when a drug is microencapsulated in a water-insoluble film, there is always concern that the drug will not be bioavailable.[8] Patricia et al[9] have attempted to form a stable pseudoephedrine-Dowex 50 WX8 complex that is less bitter in oral suspensions. The drug resin complex (DRC) particles, further coated with carnauba wax, showed fracturing of the coat necessitating impregnation, thus complicating the process feasibility. Betty et al[10] have patented a mixture of coated and noncoated sulfonic acid resins loaded with dextromethorphan for taste masking and sustained release. High-potency adsorbate of methapyrilene, dextromethorphan, and pseudoephedrine with methacrylic acid resin showed a significant reduction in bitterness of the drugs but required coating of adsorbates.[11] Researchers have reported complexation of diltiazem with carrageenan for enhanced solubility and modified release pattern.[12,13]

The purpose of this research was to formulate tasteless complexes of ciprofloxacin with Indion 234 and evaluate molecular properties of drug complexes. Indion 234 is inexpensive resin, and a simple, rapid, and cost-effective

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Table 1. Calibration Curve Values for Ciprofloxacin Analysis

Serial No.	Solvent System	λ Max	Curve Details
1	Deionized water	274 nm	F_1 = 11.153 F_o = –0.055 R = 0.999 41
2	0.1 N Hydrochloric acid	278 nm	F_1 = 10.708 F_o = –0.108 R = 0.9994
3	pH 6.7 solution	271 nm	F_1 = 13.770 F_o = –0.184 R = 0.9996

method was attempted. Drug complexation with ion exchange resins is mentioned in certain patents; however, the molecular properties of drug resinate and the effect of electrolytes on drug release from complex has not been investigated much.[14] The natural variations in pH can be used advantageously to prepare complexes that remain stable in the mouth without affecting gastric release. Ciprofloxacin has requisite aqueous solubility, pK_a (5.61-6.18) and exchangeable secondary amine moiety. Indion 234, a water-insoluble, high molecular weight, polycarboxylic acid resin is a highly porous indigenous resin. A batch process of complexation is optimized with reference to drug loading, temperature, and pH. Molecular properties of optimized complex and the effect of electrolyte on drug release are reported.

Materials and Methods

Materials

Ciprofloxacin hydrochloride (batch no. 007742001) was a gift sample from Get-Rid Pharmaceuticals (Pune, India). The resin, Indion 234 (batch no. 1092824), was procured from Ion Exchange India Ltd (Mumbai, India). Sodium chloride, calcium chloride, and other chemicals of ultrapure grade were purchased locally.

Methods

Optimization of Ciprofloxacin-Indion 234 Complexation

Preliminary Evaluation of Resin

Indion 234 particle diameter was measured microscopically. Water absorption time was obtained by keeping 500 mg of Indion 234 in contact with 1 mL of water in a Petri dish. The time required for complete water absorption was recorded. For loading capacity of resin, 1 g of resin placed in a funnel was washed with 500 mL of 1 N HCI. The filtrate was analyzed for K^+ content using a flame photometer.

Effect of Resin Activation

Indion 234 (200 mg), placed on a Whatman filter paper (Whatman Asia Pacific Pvt Ltd, Mumbai, India) in a funnel, was washed with deionized water and subsequently with 1N HCl (100 mL). The resin was rewashed with water until neutral pH was reached. DRC was prepared by placing 100 to 300 mg of acid-activated resin in a beaker containing 25 mL deionized water. Ciprofloxacin (100 mg) was added to resin slurry with magnetic stirring. On filtration, the residue was washed with 75 mL of deionized water. Unbound drug in filtrate was estimated at 274 nm. Similarly, alkali activation of Indion 234 was performed, replacing 1 N HCl with 1 N KOH. Finally, Indion 234 was also activated with combined treatment of 1 N HCl and 1 N KOH solutions. The drug-loading efficiency of activated resin was evaluated spectrophotometrically (standard curve, Table 1).

Effect of Swelling of Resin on Drug Loading

Separate batches of activated Indion 234 (200 mg) were soaked in 25 mL of deionized water contained in a beaker for 10, 20, 30, and 40 minutes, respectively. The complexation in batch process was performed, and the loading efficiency with resin swollen for different times was determined.

Formation of Ciprofloxacin-Indion 234 Complexes

A glass column (1.4-cm inner diameter, 20-cm length) plugged with cotton was packed with activated Indion 234 (100, 200, and 300 mg as per 1:1, 1:2, and 1:3, drug:resin ratio) by gently tapping. The 50 mL of deionized water maintained in the column was drained after 30 minutes. Aqueous drug solution (25 mL as per ratio), added in small portions on top of column, was left to equilibrate for 60 minutes. The solution was drained, and DRC was washed with 500 mL deionized water. Unbound drug from filtrate was estimated at 274 nm.[15]

In a batch process, 100 mg of activated resin was placed in a beaker containing 25 mL of deionized water and allowed to swell for 30 minutes. Accurately weighed ciprofloxacin (as per 1:1, 1:2, and 1:3, drug:resin ratio) was added and stirred for 30 minutes. The mixture was filtered and residue was washed with 75 mL of deionized water. Unbound drug in filtrate was estimated at 274 nm and drug-loading efficiency was calculated.

Optimizing Drug Loading (Batch Process)

Accurately weighed ciprofloxacin (100 mg) was added to 130 mg of activated resin and slurred in 25 mL of deionized water. Six batches with a stirring time of 5, 10, 15, 20, 30, and 240 minutes were processed. Amount of bound drug at

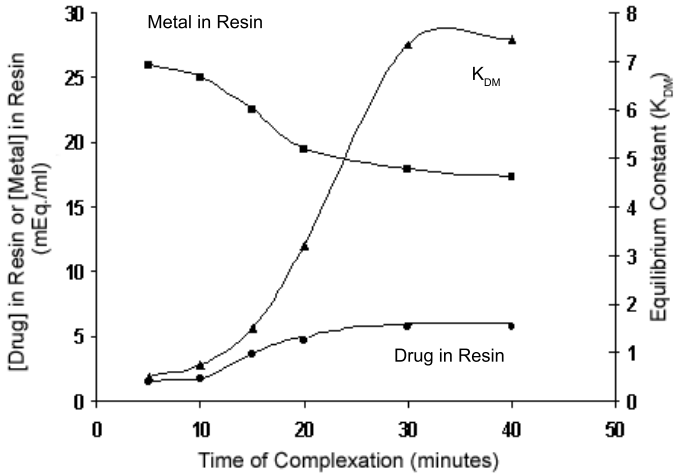

Figure 1. Equilibrium constant of ciprofloxacin complexation with time.

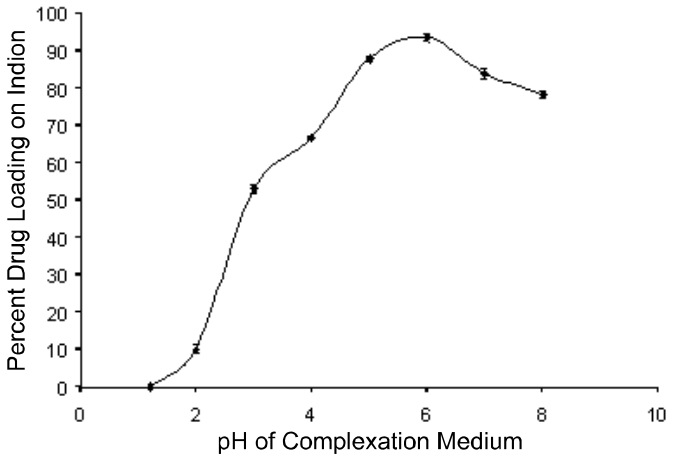

Figure 2. Effect of reaction medium pH on ciprofloxacin-loading efficiency.

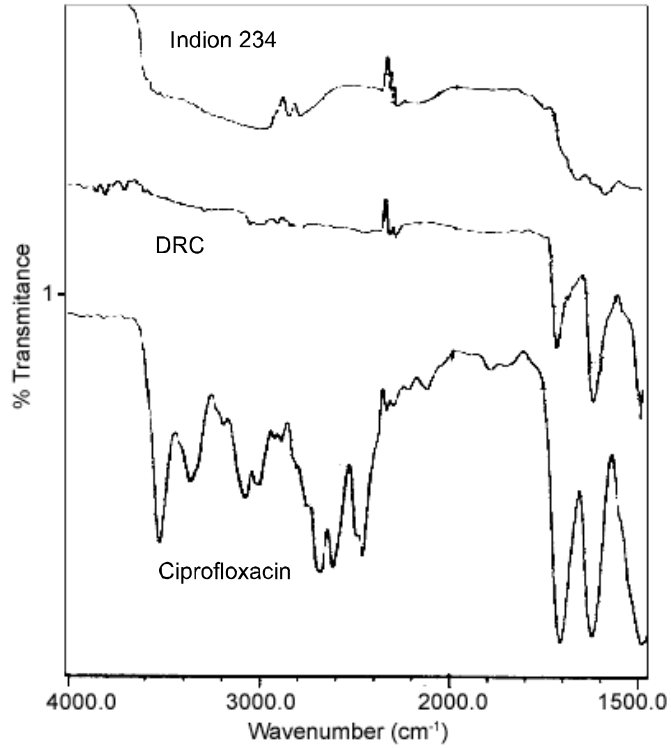

Figure 3. Infrared spectra of Indion 234, DRC, and ciprofloxacin.

the end was estimated at 274 nm. In equilibrium exchange studies (performed simultaneously, Figure 1), the amount of K^+ in Indion 234 displaced by drug with time was analyzed.[16] Equilibrium constant K_{DM} was calculated using Equation 1.

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

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

Effect of Temperature and pH on Complex Formation

The complexation of 100 mg of drug with 130 mg of activated resin, slurred in 25 mL of deionized water in a 100 mL beaker, was performed at 27°C, 40°C, 60°C, and 80°C using temperature-controlled magnetic stirring for 30 minutes. The volume of filtrate was made up to 50 mL with water washings of DRC. The amount of bound drug was estimated spectrophotometrically (274 nm) from the unbound drug in filtrate.

Accurately weighed, 100 mg of drug powder was added to 130 mg of activated resin slurred in 25 mL each of pH 1.2, 2, 3, 4, 5, 6, 7, and 8 solutions prepared from standard solutions of hydrochloric acid and sodium hydroxide in a 100-mL beaker, and maintained at 25°C. The drug-loading efficiency was estimated (see Figure 2).

Molecular Properties of Drug Resin Complex

Infrared spectra of DRC, drug, and physical dispersion (optimized ratio) thereof were obtained using Fourier-transform infrared (FTIR) spectroscopy (Jasco V5300, Tokyo, Japan). The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 1500 cm^{-1}. The 3 spectra were comparatively analyzed (Figure 3).

The powder x-ray diffraction patterns (XRPD) of the physical mixture (1:1.3) of ciprofloxacin and Indion 234, and DRC were recorded using Philips PW 1729 x-ray diffractometer (Legroupe Interconnexion, Saint Jurie, Clubac, Canada). Samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 50° and 2° (2θ). The voltage and current applied were 30 Kv and 30 mA, respectively, while the range of 5×10^3 cycle/s and chart speed of 100 mm/2θ were used (Figure 4).

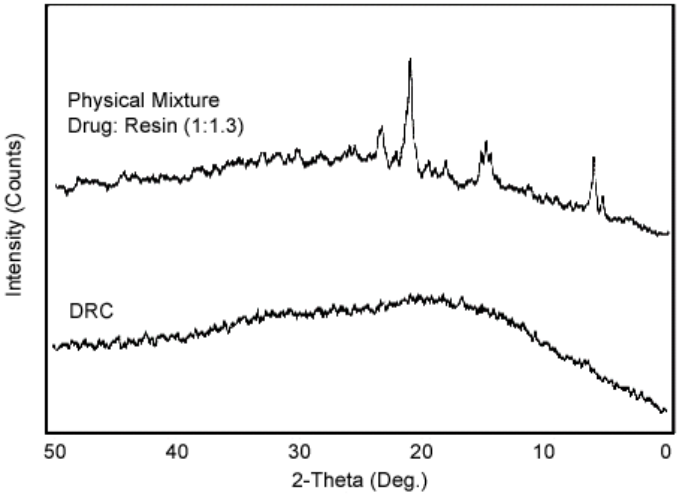

Figure 4. XRPD of physical mixture of ciprofloxacin-Indion 234 (1:1.3) and DRC.

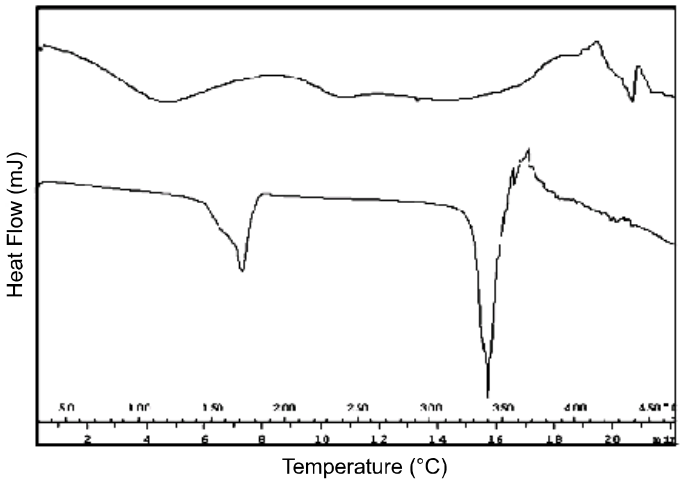

Figure 5. DSC curves for DRC and ciprofloxacin.

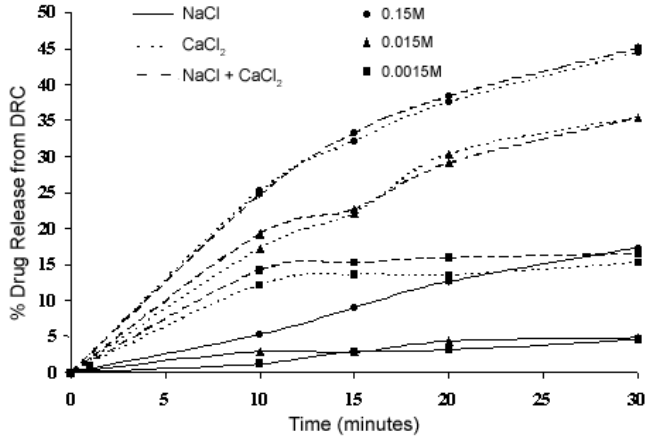

Figure 6. Effect of electrolytes on ciprofloxacin release from complexes.

A Mettler Toledo differential scanning calorimeter (DSC) 821 (Mettler Toledo, Greifensee, Switzerland) equipped with an intracooler and a refrigerated cooling system was used to analyze the thermal behavior of ciprofloxacin and DRC. Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50 mL/min and 100 mL/min through cooling unit. The thermal behavior of hermetically sealed samples (5-10 mg) heated at 20°C/min is shown in Figure 5.

Taste evaluation of DRC was performed by volunteers in the age group of 19 to 22 years. Bharati Vidyapeeth Ethical Committee (constituted as per guidelines of Medical Council of India) approved the taste evaluation in volunteers. The study protocol was explained and written consent was obtained from volunteers. DRC equivalent to 500 mg ciprofloxacin was held in the mouth for 15 seconds by each volunteer, and the bitterness level was recorded against pure drug using a numerical scale.[17]

Drug Release From DRC

Drug release from DRC (1:1.3) in deionized water was determined using a United States Pharmacopeia (USP) 24 type II dissolution apparatus. DRC equivalent to 500 mg of drug was weighed accurately and added to 900 mL deionized water and maintained at 37°C. Drug release was performed at 100 rpm for 30 minutes. A 2-mL sample removed from mixtures each kept at 5 to 30 minutes was filtered, and the amount of drug was estimated spectrophotometrically. Similarly, drug release from DRC was performed at pH 1.2, replacing deionized water with 900 mL of 0.1 N HCl for 120 minutes. Drug release from the DRC was also performed in 10 mL of pH 6.7 solution by adding 500 mg of the DRC to a test tube. The mixture was filtered after shaking for 60 seconds. The filtrates were assayed for drug.

Drug release from DRC was performed in NaCl solutions (0.0015 M, 0.015 M, and 0.15 M) using USP 24 type II dissolution apparatus (37°C, 900 mL, 100 rpm) for 30 minutes. Similar study was performed in $CaCl_2$ solutions (0.0015 M, 0.015 M, and 0.15 M) and in a combined solution containing identical strength of both NaCl and $CaCl_2$ (0.0015 M, 0.015 M, and 0.15 M). The effect of electrolytes on drug release from DRC is shown in Figure 6.

Results and Discussion

Optimization of Ciprofloxacin-Indion 234 Complexation

Ciprofloxacin hydrochloride, a broad-spectrum antibiotic, prescribed extensively in both solid and liquid dosage forms, is extremely bitter resulting in poor patient compliance. Complexation with ion exchange resin is a simple and efficient technique of masking the bitterness. The drug being soluble in water has 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 taste masking. 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 seconds. Indion 234 is highly porous, and even though insoluble in water, it is capable of hydration. Loading capacity of Indion 234 is a function of exchange of K+ ions in the resin with ions in solution. The loading capacity of 10.4 mEq/g was confirmed.[18]

The percentage drug loading with inactivated resin, treated with acid, alkali, and combination thereof was found to be 67.05% ± 1%, 93.48% ± 1.15%, 93.55% ± 1.2%, and 96.14% ± 0.30% wt/wt, respectively. Highest drug binding on resin was achieved when activated with both acid-alkali treatments. Impurity associated with industrial scale manufacture or absorbed during storage or handling may be neutralized by treating with combined solution. The combined resin activation exposed the exchangeable groups producing rapid drug exchange and hence higher drug binding.

Ciprofloxacin may be loaded on Indion 234 by batch or column process. The drug-loading efficiency for a drug-resin ratio 1:1, 1:2, and 1:3 of column process was 89.54% ± 1.59%, 95.67% ± 1.16%, and 95.67% ± 0.88% wt/wt and that of batch process was 92.34% ± 0.98%, 96.26% ± 0.88%, and 96.50% ± 1.10% wt/wt. A 4% wt/wt increase of loading efficiency was observed in batch process, when drug-resin ratio was changed from 1:1 to 1:1.2. Hence the drug loading performed at intermediate drug-resin ratio of 1:1.3, 1: 1.5, and 1:1.7 was found to be 95.36% ± 1.10%, 95.76% ± 1.01%, and 95.60% ± 1.67% wt/wt, respectively. Although drug binding was comparable, batch process was simpler and quicker than the column process (2 hours). Difficulty was experienced in handling small particles in the column process. Ciprofloxacin dose ranging from 250 to 700 mg and the higher resin ratio in the latter 2 (1:1.5 and 1:1.7) would be difficult to accommodate in tablet and suspension formulations. The drug-resin ratio of 1:1.3 has optimum drug loading. Santos and Ghaly[19] have reported a loading efficiency of 38.6% for cimetidine using amberlite 69. In the case of ciprofloxacin hydrochloride and Indion 234 a drug-loading efficiency of more than 92% wt/wt was achieved even with a drug-resin ratio of 1:1.

Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution.[20] As the reaction is an equilibrium phenomenon, maximum efficacy is best achieved in batch process. Equilibration time was shorter due to thinner barrier for diffusion of ions, as it is in continuous motion. Also, higher swelling efficiency in the batch process results in more surface area for ion exchange. Hence, the batch process is suitable for smaller particles.

Indion 234, unswollen, and swollen 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. The swelling and hydrating properties of Indion 234 affect the rate of ion exchange, which in turn affects the percentage drug loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency.[21] The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. The percentage drug loading (wt/wt) with a stirring time of 5, 10, 15, 20, 30, and 240 minutes was found to be 50.20% ± 1.31%, 56.25% ± 1.10%, 71.27% ± 1.04%, 93.53% ± 0.63%, 95.50% ± 0.62%, and 95.63% ± 0.66%, respectively. Figure 1 shows results of equilibrium study performed simultaneously. This study revealed that as time increased, the K_{DM} values increased rapidly up to 20 minutes. Although the K^+ release is not much seen after 20 minutes, it is surprising to note the high exchange rate between 20 and 30 minutes. This finding may indicate the significant involvement of van der Waals forces or chemisorption taking place along with drug exchange during complexation.[22] Increasing the stirring time above 30 minutes did not further increase the K_{DM} values. Hence, 30-minute contact time between drug and resin could be optimized to equilibrate the ion exchange process to achieve maximum drug loading. This study indicated that the optimum ion exchange could be completed in a short period of 30 minutes.

Efficient drug loading on Indion 234 occurred uniformly (95.25% ± 0.45% wt/wt) in the experimental temperature range of 27ºC to 80ºC. Drug adsorbate formation may be significantly affected by processing temperature. Increased temperature during complexation increases ionization of drug and resin. The effect is more pronounced for poorly water soluble and un-ionizable drugs. Higher temperatures tend to increase the diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. Frank and Koebel[23] reported that cation exchangers are not affected as significantly by temperature changes as anion exchange resins. In the case of drug-resin adsorbate formation, ciprofloxacin hydrochloride is a water-soluble drug with a pK_a of 5.61 to 6.18 that has potential at operational pH to be completely ionized. The continuous stirring in batch process does not allow development of thick exchange zones. This finding explains why temperature does not show any effect on ciprofloxacin-Indion 234 complexation.[24]

Ciprofloxacin-Indion 234 complexation involves the exchange of ionizable drug and metal ions in resin, which in turn depends on the pK_a of drug and resin. Such a mode of complexation between amino group of ciprofloxacin and –COO-K+ functionality of Indion 234 can be affected by the pH of the reacting media. The complexation was enhanced with increasing pH from 1.2 to 6. A maximum of 94.3%

wt/wt drug loading was obtained at pH 6 (ie, at pK_a of ciprofloxacin hydrochloride). As shown in Figure 2, as pH increased above 6, the percentage drug loading decreased. The pH of the solution affects both solubility and the degree of ionization of drug and resin. The results can be attributed to the fact that ciprofloxacin hydrochloride has a pK_a between 5.61 and 6.18 and hence will have maximum solubility and complete ionization in this range. The decreased complexation at lower pH is due to excess H^+ ions in the solution, which have more binding affinity to the $–COO^–$ groups of resin and compete with the drug for binding. Such a trend was also reported in complexation of chloroquine phosphate with a polymethacrylic acid cation exchange.[21] The study revealed negligible effect of higher temperature on drug loading, while the pH of media significantly altered the ion exchange complexation process.

Molecular Properties of Drug-Resin Complexes

The infrared spectra of Indion 234, ciprofloxacin-Indion 234 complex and ciprofloxacin hydrochloride are depicted in Figure 3A, B, and C, respectively. Drug spectrum shows a prominent peak at 3375.2 cm^{-1} corresponding to the NH stretching in a secondary amine. Figure 3C shows peaks corresponding to –COOH dimerization of drug in the range of 2464.9 to 3091.7 cm^{-1}. Dimerization is a characteristic of acidic functionality, where the compound occurs in the form of dimers of acids due to self-association in the drug molecule through weak van der Waals forces. A peak at 3535 cm^{-1} is due to –OH stretching, which lies in standard range of 3400 to 3600 cm^{-1}. Indion 234 shows characteristic peaks at 1674 cm^{-1}, at 1764 cm^{-1} corresponding to –C = O stretching of aryl acids, and at 1602 cm^{-1} due to aromatic C = C stretching. Numbers of overtone peaks were observed at 2308 and 2347 cm^{-1}. The absence of peak at 3375 cm^{-1} in DRC (1:1.3) confirms the complexation of the secondary amine group in the drug with resin. The absence of peaks (3091-2464 cm^{-1}) due to dimerization of carboxylic acid groups in the drug in DRC denotes the breaking of acid dimers during complexation. The peak at 3535 cm^{-1} in DRC corresponding to –OH stretching is also absent, which signifies that during DRC formation there was interaction of the amino group of drug with the carboxylic group of Indion.[25]

Ciprofloxacin hydrochloride is crystalline, while Indion 234 is amorphous resin. XRPD of the physical dispersion of drug and resin and DRC is shown in Figure 4. The physical dispersion of drug and resin shows a sum of several sharp peaks owing to the crystal nature of ciprofloxacin and some diffused peaks of the amorphous resin. The molecular state of the drug prepared as DRC shows a hollow diffused pattern and the absence of drug peaks. This finding confirms that the entrapped drug is dispersed monomolecularly in the resin bead. In the case of physical dispersions of drug and Indion 234, drug molecules are outside the resin bead. Thus, DRC is amorphous in nature and shows faster dissolution due to improved solubility. In addition, amorphous compounds have increased water absorption time (confirmed to be 45 seconds versus 147 seconds for physical mixture (1:1.3, drug:resin).

Figure 5 shows DSC curves for DRC (top) and pure ciprofloxacin hydrochloride (bottom). The thermal behavior of the pure drug shows endotherms at 168.88°C and 335.00°C corresponding to loss of water of crystallization and melting of pure drug. The thermal behavior of DRC shows fractional loss of water between 100°C and 140°C and melting endotherm of drug at 335°C. However, the DRC curves show a small gradual exotherm at 428°C indicating onset (endothermic-exothermic inversion) and gradual decomposition of the optimized complex. The study confirms the complexation of ciprofloxacin with Indion 234, and the DSC and XRPD results reveal the amorphous nature of drug adsorbates.

Drug Release From Drug-Indion Complex

Ciprofloxacin release from drug-resin adsorbate was observed in deionized water for 30 minutes, in average salivary pH of 6.7, and at gastric pH of 1.2, separately. Less than 0.2% wt/vol of drug was released in deionized water in 30 minutes, indicating the stability of complexes and suitability for reconstitutable suspensions. In vitro drug release in average salivary pH of 6.7 was less than 5% within 60 seconds. The presence of exchangeable ions of ionizable electrolytes in the salivary fluid may be responsible for this release. The DRC is stable in salivary pH for a period of administration. The amount released is insufficient to impart bitter taste while the formulation passes through the mouth to further parts of the gastrointestinal (GI) tract. At gastric pH (1.2), 59% of ciprofloxacin was released within 15 minutes, and the release was complete in 120 minutes. The hypothesis that the drug-release equilibrium, similar to drug loading, is highly dependent on the physiological pH can be applied for taste masking without affecting the dosage form characteristics.

The exchange process of drug release follows Equation 2.

$$Resin^- – Drug^+ + X^+ \rightarrow Resin^- – X^+ + Drug^+, \qquad (2)$$

where, X^+ represents the ions in the GI tract.

Particle diffusion and film diffusion are sequential steps in drug release by ion exchange process.[26] Indion 234-ciprofloxacin complex hydrates by water absorption and then swells in diffusion media, and 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. Drug release at pH 6.7 and cation concentration of 40 mEq/L in a short period of ingestion does not alter the exchange process. The complexation of ciprofloxacin hydrochloride with Indion 234 produces amorphous tasteless drug resonates. Taste evaluation in volunteers confirmed that the taste of ciprofloxacin was masked by complexing with Indion 234. The majority of the volunteers found the DRC to be tasteless and agreeable. When DRC is exposed to a low pH, it causes dissociation of the complex. The presence of H^+ ion in the medium causes displacement of ciprofloxacin, thus facilitating drug release. This finding has been well supported by XRPD and DSC data and confirmed by in vitro drug release in salivary pH.

Figure 6 shows the effect of the ionic strength of salts on drug release from DRC. It may be noted that an insignificant amount of drug was released (0.2%) in plain deionized water. The drug release from complex increased as the concentration of electrolyte increased in the medium. In a solution of 0.0015 M and 0.015 M NaCl, drug release showed insignificant difference. However, increased release of 17.3% was observed in 0.15 M NaCl solution. Similarly, increasing the $CaCl_2$ concentration in the medium increased the drug release from DRC. The effect of divalent calcium ions was more pronounced than monovalent sodium ions. Drug release of 15%, 35%, and 45% within 30 minutes was observed with respect to 0.0015 M, 0.015 M, and 0.15 M $CaCl_2$ in solution.

Electrostatic interactions govern the equilibrium distribution of the drug species between the resin and solution phases.[27-29] Increasing the electrolyte concentration decreases the Donnan potential and, hence, the electrostatic affinity between the drug and the ion exchanger, thus tending to increase drug release. The influence of salt concentration on the release rate can be explained by solute diffusion. The ciprofloxacin release from DRC is controlled by an ion exchange mechanism. The exchange rate is dominated by the rate at which the competing ions diffuse from the media to resin. Solute diffusion is driven by concentration gradient. At high salt concentration, the concentration gradient is greater, resulting in faster diffusion of ions, and thereby a higher release rate. Valency of the counter ions influence exchange capacity. The rate of sorption of the divalent calcium ions was much faster as compared with Na^+ ions, which are less firmly bound. Also, the selectivity of carboxylic acid resins is higher for divalent calcium ions. Even though larger size Ca^{2+} ions are expected to diffuse slowly, its valency enhances the drug release. Calcium ions also reduce the Donnan potential to greater extent. Drug release at low electrolyte concentration of either sodium chloride or calcium chloride is controlled by normal particle diffusion mechanism. At higher electrolyte concentrations (in both NaCl and $CaCl_2$) of 10^{-3} M to 10^{-2} M, the resin bead is invaded by co-ions and neutralization proceeds inside the resin particles. This increases DRC matrix porosity and hence the exchange rates. Drug release is a reverse process to drug loading; both involve ions that compete for ionic binding sites with the drug.

Conclusion

The batch process of complexing ciprofloxacin with Indion 234 produced efficient drug loading. The process of complexation completely inhibited the crystallinity of ciprofloxacin and revealed the amorphous nature of the complex. The drug release from the DRC increased with the salt concentration, and the effect was more pronounced with divalent calcium ions. The volunteers rated the complexes as tasteless and agreeable.

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