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# Characterization of adsorption behavior by solid dosage form excipients in formulation development

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## Summary

The adsorption of drugs onto solid dosage form excipients may influence dissolution characteristics, analytical testing and bioavailability. CI-977 ([5*R*-(5$\alpha$,7$\alpha$,8$\beta$)]-*N*-methyl-*N*-[7-(pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide monohydrochloride), a $\kappa$-opioid agonist analgesic compound, was found to adsorb onto microcrystalline cellulose, croscarmellose and sodium starch glycolate. The extent of adsorption was affected by pH, ionic strength and ionic species. The adsorptive capacity and relative affinity for CI-977 adsorption to microcrystalline cellulose was characterized under various experimental conditions using Langmuir isotherms. The results show that electrolytes inhibit adsorption by reducing both the affinity of the adsorbent for the adsorbate and the adsorptive capacity of the adsorbent. Divalent cations reduced the adsorption to a greater extent than monovalent cations. The effects of pH and electrolytes suggest that the predominant mechanism of CI-977 adsorption to microcrystalline cellulose is electrostatic attractive forces.

## Introduction

CI-977 (Fig. 1; [5*R*-(5$\alpha$,7$\alpha$,8$\beta$)]-*N*-methyl-*N*-[7-(pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide monohydrochloride) is a centrally acting $\kappa$-opioid agonist intended for use as an analgesic in the treatment of mild to moderate pain. The hydrochloride salt form of the compound (p$K_a$ 8.8) was found to be soluble (> 200 mg/ml) and thermally stable. Based on pharmacological screens, the projected oral human dose is less than 1 mg. In the present study, the adsorption of CI-977 to solid dosage form excipients was studied in order to determine its significance in formulation development.

In the development of oral formulations many factors must be considered. They include: (1) the drug should be stable in the presence of formulation excipients; (2) the drug should be recovered from the formulation excipients; (3) the drug should exhibit acceptable dissolution characteristics from the formulation; (4) processing should allow for acceptable content uniformity; and (5) the formulation should have acceptable physical characteristics. Many of these aspects are ad-

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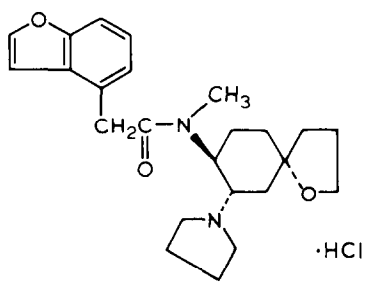

Fig. 1. Structure of CI-977 ([5*R*-(5$\alpha$,7$\alpha$,8$\beta$)]-*N*-methyl-*N*-[7-(pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide monohydrochloride).

dressed in preformulation through drug-excipient compatibility studies (Carstensen, 1990). Chemical stability is often the primary concern with drug-excipient compatibility evaluations. However, the drug-excipient physical interactions can also affect the formulation performance and the development of analytical methodology. For instance, although the interactions resulting in the adsorption of drugs onto solid dosage form excipients are generally of a weak type such as van der Waals forces and hydrogen bonding, they have been shown to influence dissolution characteristics (Aboutaleb et al., 1986; Aly and Udeala, 1987) and bioavailability (Calis et al., 1986; El Gamal et al., 1986; Aly and Megwa, 1987). Adsorptive behavior can also affect content uniformity following a wet granulation process. Zografi and Mattocks (1963) have shown that the migration of water-soluble dyes during tablet manufacture can be related to adsorption with excipients. Additionally, analytical methods must be developed taking drug-excipient adsorptive behavior into account to ensure accurate assays (Pramar and Gupta, 1991). Subsequently, it is important to characterize drug-excipient adsorption behavior during formulation development.

## Experimental

*Materials*

CI-977 was supplied by Parke-Davis Pharmaceutical Research (Ann Arbor, MI). Microcrystalline cellulose, N.F. (Avicel PH 102) and croscarmellose sodium, N.F. (Ac-Di-Sol) were obtained from FMC Corp.; pregelatinized starch, N.F. (National 1551) from National Starch and Chemical Co.: corn starch N.F. from Husinger Co.; dicalcium phosphate dihydrate USP from Stauffer Chem. Co.; lactose, N.F. (Fast-Flo) from Van Waters and Rogers, Inc.; magnesium stearate N.F. from Mallinckrodt, Inc.; and sodium starch glycolate, N.F. (Explotab) from Edward Mendell Co. Single lots of each excipient were used throughout this study.

*Analytical methods*

CI-977 was assayed by an HPLC method. The HPLC system was comprised of a Hewlett Packard HP1090 liquid chromatograph, a Kratos 783 variable-wavelength detector (equipped with a 2.4 $\mu$l flow-cell, $\lambda$ = 250 nm), a Hewlett Packard HP3393A computing integrator, and a Beckman ODS (250 × 2.0 mm, 5 $\mu$m) column. Two sets of chromatographic conditions were employed. The first consisted of a mobile phase containing 0.05 M triethylamine adjusted to pH 3 with phosphoric acid (75%), tetrahydrofuran (12.5%) and acetonitrile (12.5%) with a flow rate of 0.2 ml/min. An alternative mobile phase was used to separate chromatographic interference caused by pregelatinized starch, corn starch and dicalcium phosphate dihydrate. This mobile phase consisted of 0.05 M triethylamine/0.05 M ammonium dihydrogen phosphate/0.025 M sodium octanesulfonate adjusted to pH 3 with phosphoric acid (70%) and acetonitrile (30%) with a flow rate of 0.6 ml/min.

*Evaluation of potential for CI-977 to adsorb to excipients*

The potential for microcrystalline cellulose, dicalcium phosphate dihydrate, croscarmellose sodium, sodium starch glycolate, corn starch and pregelatinized starch, to adsorb CI-977 was evaluated using the following procedure. 50 mg of excipient (10 mg of sodium starch glycolate was used due to its gelation properties) was placed into 1.5 ml polypropylene centrifuge tubes. 1 ml of a stock solution composed of either water (pH 5.8), phosphate buffer (0.05 M, pH 7.0), citrate buffer (0.05 M, pH 5.0), 0.9% NaCl or 0.1 N HCl

containing 1.0 μg/ml of CI-977 was added to each tube. The samples were shaken for 1 h (ambient temperature) using a rotary shaker (IKA-Vibrax-VXR, IKA-Works, Inc.). Controls (without excipients) were treated identically. Following the 1 h equilibration period, the samples were centrifuged (Eppendorf Centrifuge 5415C) and the supernatants were assayed. The recovery was determined as the peak response compared with controls. Samples were prepared and evaluated in duplicate.

*Preparation of powder blends and dissolution analysis*

Three powder blends containing 10 mg CI-977/200 mg blend were prepared by geometric trituration in a mortar. The formulation compositions were (blend A) microcrystalline cellulose/croscarmellose (2%)/magnesium stearate (0.25%); (blend B) lactose (spray dried)/pregelatinized starch (10%)/magnesium stearate (0.25%); and (blend C) dicalcium phosphate dihydrate/pregelatinized starch (10%)/magnesium stearate (0.25%). The powder blends were hand-filled into hard gelatin capsules (200 mg blend/capsule). The capsule sizes used were nos 1, 3 and 2 for capsule blends A, B and C, respectively. Dissolution behavior was evaluated in distilled water using USP Method II. Samples were intermittently withdrawn over a 2 h time period and assayed by HPLC.

*Characterization of CI-977 adsorption to microcrystalline cellulose*

The effects of ionic strength and pH on adsorption of CI-977 were evaluated using microcrystalline cellulose as the model adsorbent. The effect of electrolyte was determined using the following procedure. A series of CI-977/microcrystalline cellulose suspensions were prepared by the addition of 10 ml of a CI-977 stock solution (5, 10, 25, 50, and 100 μg/ml) to 20 ml glass vials containing 0.5 g of microcrystalline cellulose. The CI-977 stock solutions were prepared in distilled water without ionic strength adjustment, and also in distilled water with the ionic strength adjusted to 0.0005 and 0.001 with either sodium chloride or calcium chloride. The degree of ionic

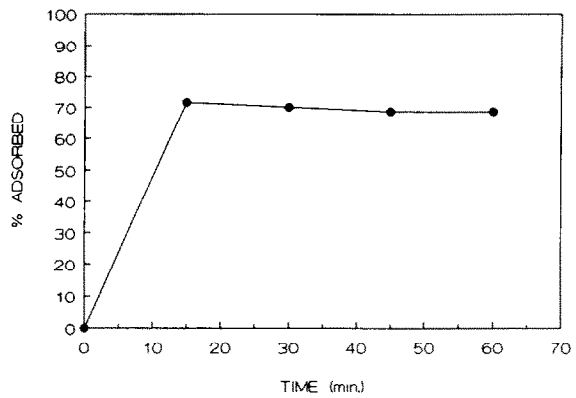


Fig. 2. Typical plot indicating equilibrium adsorption occurred within 15 min. Experimental conditions were: 0.5 g of microcrystalline cellulose dispersed in 10 ml of CI-977 stock solution (5 μg/ml, distilled water).

strength adjustments was made on the basis of preliminary adsorption experiments, which indicated that limited adsorption occurred at higher ionic strengths. The vials were equilibrated for 1 h at 25 ± 0.5°C on a mechanical shaker water bath (Versa-Bath S, Fisher Scientific). Preliminary experiments established that equilibrium adsorption was reached within 15 min (Fig. 2). Following the 1 h equilibration period, samples were centrifuged at 25 ± 1.0°C (BHG Hermle Z 360 K centrifuge) and the supernatants were assayed by HPLC to determine the equilibrium concentration. Samples were prepared and evaluated in duplicate.

The effect of pH was evaluated using the following procedure. CI-977/microcrystalline cellulose suspensions were prepared and evaluated by the method stated above. Stock solutions containing 50 μg/ml CI-977 were used for the pH effect studies. The pH of the stock solutions was adjusted using 0.1 N HCl or 0.1 N NaOH. An appropriate amount of sodium chloride was added to adjust the ionic strength of each stock solution to 0.001. The pH of each suspension was determined following the equilibration period. Adsorption was evaluated in the pH range 3–10. CI-977 is stable over the experimental time period under these conditions. Samples were prepared and evaluated in duplicate.

## Results and Discussion

The results of the evaluation of the potential for CI-977 to adsorb to excipients are listed in Table 1. As can be seen, complete recovery of CI-977 was not achieved from microcrystalline cellulose, croscarmellose or sodium starch glycolate suspensions in water. However, the adsorption was eliminated in the case of microcrystalline cellulose and reduced in the cases of croscarmellose and sodium starch glycolate from phosphate buffer (0.05 M, pH 7.0), citrate buffer (0.05 M, pH 5.0), 0.1 N HCl and 0.9% NaCl solutions. In this way, it was demonstrated that analytical methods and formulation development should take the physical interactions between CI-977 and solid dosage form excipients into account. Adsorption behavior is often the result of hydrophobic interactions with lipophilic compounds. The propensity for adsorption of a drug has been related to the oil/water partition coefficient as a measure of the lipophilicity (Fung, 1990). The solubility of CI-977 suggests that mechanisms other than hydrophobic interactions contribute to adsorption to these solid dosage form excipients.

The protocol in which the excipients were evaluated for potential to adsorb CI-977 represented exaggerated experimental conditions in terms of CI-977/excipient and excipient/medium volume ratios. The influence of excipient adsorption on dissolution analysis in water of powder blends is shown in Fig. 3. The powder blend containing microcrystalline cellulose and croscarmellose (powder blend A) exhibits a rapid dissolution phase followed by a slow, incomplete dissolution phase over 2 h. Capsule blends containing excipients without potential to adsorb CI-977 (powder blends B and C) exhibit rapid and complete dissolution (within 15 min). The results with each powder blend are consistent with the previous results in that excipients with potential to adsorb CI-977 cause a delay in dissolution. The dissolution behavior from powder blend A is unacceptable, considering the high solubility of the compound.

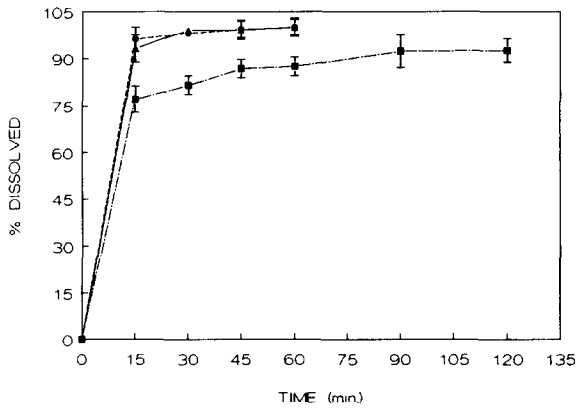


Fig. 3. Dissolution of CI-977 from powder blends. (■) Blend A, (●) blend B, (▲) blend C.

The results of the evaluation of excipients for potential to adsorb CI-977 suggest a relationship between electrolytes and pH with the extent of

TABLE 1

*Summary of recovery data from the evaluation of CI-977 adsorption to excipients*

| Excipient [b] | Fraction of CI-977 recovered [a] | | | | |
|---|---|---|---|---|---|
| | Water pH 6.0 | Phosphate pH 7.0 | Citrate pH 5.0 | HCl pH 1.1 | NaCl pH 5.9 |
| Microcrystalline cellulose | 0.34 | 0.99 | 1.00 | 1.01 | 0.99 |
| Dicalcium phosphate dihydrate | 1.02 | – | – | – | – |
| Croscarmellose | 0.22 | 0.63 | 0.68 | 0.74 | 0.72 |
| Sodium starch glycolate | 0.60 | 0.94 | 0.95 | 1.00 | 0.95 |
| Pregelatinized starch | 1.00 | – | – | – | – |
| Corn starch | 0.99 | – | – | – | – |

[a] Fraction of CI-977 recovered from suspensions containing 1 μg/ml of CI-977. Values represent the mean fractional peak response ($n = 2$) compared with controls (without excipients).

[b] Suspensions were prepared using 50 mg of excipient except for sodium starch glycolate in which 10 mg was used.

adsorption. In order to determine potential adsorption mechanisms and the significance of CI-977 adsorption to the development of solid dosage forms, the adsorption of CI-977 to microcrystalline cellulose was further characterized. The effect of added electrolyte on adsorption was evaluated using Langmuir isotherms. The equilibrium concentration ($C_{eq}$, mg/100 ml) and the amount of drug adsorbed in mg per g of microcrystalline cellulose ($X/M$) were determined under various experimental conditions. The adsorption isotherms are shown in Fig. 4. The linear form of the Langmuir adsorption isotherm is given by:

$$\frac{C_{eq}}{X/M} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2} \qquad (1)$$

where $k_1$ and $k_2$ are constants. The constant $k_1$ is a measure of the relative affinity of the adsorbate for the adsorbent. The constant $k_2$ is the adsorptive capacity of the adsorbent (mg of adsorbate which can be adsorbed by 1 g of adsorbent). The linear plots of the Langmuir adsorption isotherms obtained under varied ionic conditions are shown in Fig. 5. The adsorption constants obtained from these linear fits are summarized in Table 2. This analysis of the data indicates that added electrolyte inhibits adsorption by both reducing the affinity of the adsorbent for the adsorbate ($k_1$ decreases with increasing ionic strength) and by reducing the adsorptive capacity of the adsorbent ($k_2$ decreases with increasing ionic strength). The results also demonstrate that the extent of adsorption (in terms of both $k_1$ and $k_2$) was more sensitive to the divalent cation ($Ca^{2+}$) than the monovalent cation ($Na^+$).

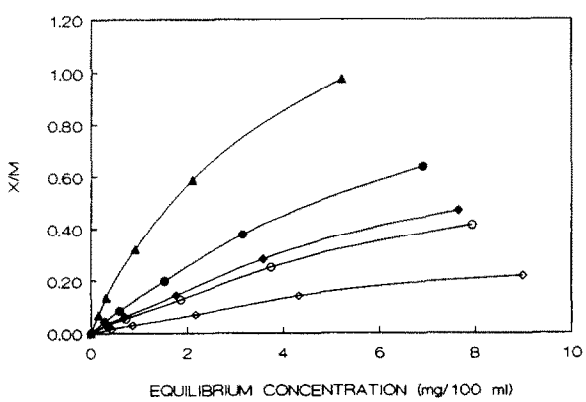


Fig. 4. Adsorption isotherms of CI-977 on microcrystalline cellulose where ionic strength and ionic species was varied. (▲) Distilled water; (●) NaCl solution, $\mu = 0.0005$; (◆) NaCl solution, $\mu = 0.001$; (○) $CaCl_2$ solution, $\mu = 0.0005$; (◇) $CaCl_2$ solution, $\mu = 0.001$.

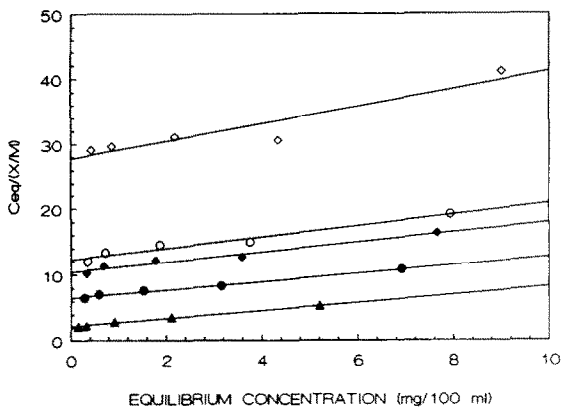


Fig. 5. Langmuir plots of CI-977 on microcrystalline cellulose where ionic strength and ionic species was varied. (▲) Distilled water; (●) NaCl solution, $\mu = 0.0005$; (◆) NaCl solution, $\mu = 0.001$; (○) $CaCl_2$ solution, $\mu = 0.0005$; (◇) $CaCl_2$ solution, $\mu = 0.001$.

Adsorption mechanisms have been previously attributed to electrostatic attractive forces between a drug and an adsorbent (Carstensen and Su, 1971; Franz and Peck, 1982; Hollenbeck, 1983). Carboxyl groups ($pK_a \cong 4.0$; Edelson and Hermans, 1963) can be formed on the surface of microcrystalline cellulose by oxidation of the hydroxy groups on individual anhydro-glucose units

TABLE 2

*Summary of constants obtained from linear plots of the Langmuir equation for CI-977 adsorption to microcrystalline cellulose*

| | Ionic strength | | | | Distilled water |
|---|---|---|---|---|---|
| | 0.001 | | 0.0005 | | |
| Ionic species: | NaCl | $CaCl_2$ | NaCl | $CaCl_2$ | |
| $k_1$ | 0.0709 | 0.0481 | 0.0936 | 0.0689 | 0.271 |
| $k_2$ | 1.35 | 0.748 | 1.62 | 1.18 | 1.65 |
| $r^2$ | 0.965 | 0.879 | 0.991 | 0.957 | 0.996 |

(McBurney, 1954; Edelson and Hermans, 1963; Mark, 1965; Franz and Peck, 1982). Hence, at pH > 4.0 the surface of microcrystalline cellulose becomes negatively charged due to ionization of the carboxyl groups. An adsorption mechanism based on ionic interactions can be described in its simplest form (constant stoichiometry, i.e., 1:1) by the following relationship

$$[X^-] + [Y^+] \leftrightharpoons [X - Y]$$

where $[X^-]$, $[Y^+]$ and $[X - Y]$ represent concentrations of the anionic, cationic and bound species, respectively. This relationship defines an equilibrium adsorption constant, $K_{ad}$, for a defined set of conditions (i.e., concentration of substrates):

$$K_{ad} = \frac{[X - Y]}{[X^-][Y^+]} = \frac{[X - Y]}{(f_{X^-}[X])(f_{Y^+}[Y])} \qquad (2)$$

where $f_{X^-}$ and $f_{Y^+}$ represent the ionized fraction of [X] and [Y] at a given pH, respectively. Rearrangement leads to the following equation for the concentration of bound species ([X–Y]), assuming the stoichiometry remains constant with varying fractions of ionized species:

$$[X - Y] = K_{ad} f_{X^-} f_{Y^+}[X][Y] = K_{ad} F[X][Y] \qquad (3)$$

where $F$ represents the ionization product coefficient. The ionization product coefficient ranges from 0 to 1 and varies with pH depending on the $pK_a$ of the adsorbent and adsorbate. According to Eqn 3, the maximum adsorption will occur (when the total concentrations of adsorbent and adsorbate are kept constant) as $F$ approaches unity, since the adsorbent and adsorbate will be in their most favorable state of ionization for adsorption. The contribution of electrostatic attractive forces to CI-977 adsorption to microcrystalline cellulose was determined by evaluating the effect of pH on adsorption. The results are depicted in Fig. 6 in which the percentage of drug bound is plotted vs pH. Also shown in Fig. 6 are calculated values of the ionization product coefficient as a function of pH, based on the ionized fraction of CI-977 ($pK_a = 8.8$) and the ionized fraction of anionic surface sites (assuming carboxyl groups are present with $pK_a = 4.0$) on microcrystalline cellulose. The ionized fractions of CI-977 were calculated using the following equation:

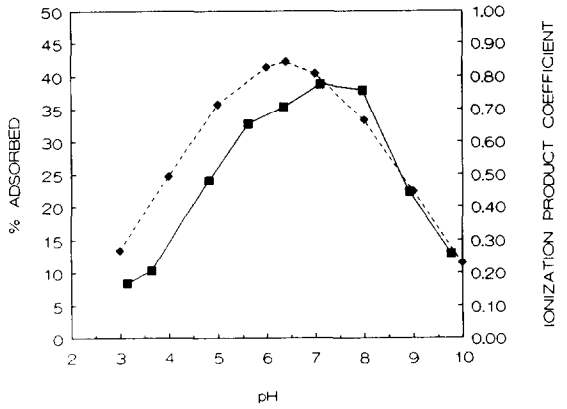


Fig. 6. Effect of pH on percent of CI-977 adsorbed (50 $\mu$g/10 ml to 0.5 g of microcrystalline cellulose). (■) % CI-977 adsorbed; (◆) calculated ionization fraction coefficient.

$$f_{Y^+} = \frac{e^{(pK_a^+ - pH)}}{1 + e^{(pK_a^+ - pH)}} \qquad (4)$$

where $pK_a^+$ represents the $pK_a$ of the cationic species (CI-977). The ionized fractions of anionic surface sites on microcrystalline cellulose were calculated using the following equation:

$$f_{X^-} = \frac{e^{(pH - pK_a^-)}}{1 + e^{(pH - pK_a^-)}} \qquad (5)$$

where $pK_a^-$ represents the $pK_a$ of the anionic species (microcrystalline cellulose). As can be seen, as the pH increases from 3 to 6, the percent of CI-977 adsorbed increases most likely due to ionization of the carboxyl groups on the cellulose surface. Likewise, as the pH increases from 8 to 10, the percent of adsorbed CI-977 decreases since less ionized drug is available. Assuming a mechanism of adsorption based on electrostatic interactions between the adsorbate and the adsorbent, an estimate of the pH where maximum

adsorption ($pH_{max}$) occurs can be calculated as the intersection of the ionized fraction curves (maximum ionisation product coefficient) for drug and anionic surface sites. An equation to calculate the intersection point can be derived by setting the equations for the respective ionized fractions equal. This yields the following equation to estimate $pH_{max}$:

$$pH_{max} = \frac{pK_a^- + pK_a^+}{2} \quad (6)$$

where $pK_a^-$ and $pK_a^+$ represent the $pK_a$ of the anionic and cationic species, respectively. The calculated $pH_{max}$ value (6.4) is dependent on the $pK_a$ estimates and does not take other adsorptive mechanisms into account, such as adsorption of the nonprotonated free base. These factors may account for a shift of the maximum adsorption observed, from the calculated $pH_{max}$ value. The maximum adsorption found experimentally was at pH 7.1.

## Conclusions

The effects of pH and electrolytes suggest that a predominant mechanism of adsorption of CI-977 to microcrystalline cellulose is electrostatic attractive forces between positively charged drug and the negatively charged surface of the microcrystalline cellulose. The adsorption capacity of microcrystalline cellulose is reduced due to increased competition between positively charged drug molecules and other cations. The adsorption of counterions can cause a reduction or a reversal of net surface charge. This could account for the reduced affinity of CI-977 for microcrystalline cellulose in the presence of additional cations (especially cations of high charge number).

Hollenbeck (1988) has shown that bioavailability of phenylpropanolamine HCl was not affected by ion-exchange interactions with croscarmellose even though a significant drug-excipient interaction was observed in distilled water. Likewise, oral bioavailability of CI-977 from formulations containing microcrystalline cellulose, croscarmellose or sodium starch glycolate may not be adversely affected, due to the pH and abundance of cations ($Ca^{2+}$, $Mg^{2+}$, $Na^+$ and $K^+$) in gastric fluid. However, adsorption to these excipients should be considered when developing in vitro testing methods (i.e., selection of dissolution medium) to ensure valid interpretation of dissolution data and accuracy of analytical methods, especially for low dose compounds such as CI-977. Subsequently, screening excipients for adsorption potential is useful in formulation development.

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