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Elimination of metformin–croscarmellose sodium interaction by competition

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Abstract

During analytical method development and validation, a strong charge interaction between metformin and croscarmellose sodium was observed when the aqueous solution containing metformin was spiked with croscarmellose sodium. The charge interaction resulted in the retention of metformin in croscarmellose sodium and caused a serious drug recovery problem. The percent recovery of metformin in the solution was much lower than its theoretical values, especially in the low metformin concentration range. To overcome the metformin–croscarmellose interaction, arginine was selected as a competitor for the binding sites on croscarmellose sodium. Because of the competition and stronger interaction between arginine and croscarmellose sodium than metformin and croscarmellose sodium, a complete recovery of metformin in presence of arginine in both low and high concentration ranges was achieved. The effect of arginine on the recovery of metformin and the competition mechanism are discussed in this paper.

Keywords: Metformin; Croscarmellose sodium; Arginine; Drug–excipient interaction; Competitor–excipient interaction

1. Introduction

Excipients formulated with drug substances are classified according to their functionalities as diluents, disintegrants, fillers, binders, and lubricants. Traditionally, excipients are pharmacologically inert components in formulations. However, many reports in the last few decades showed that excipients can physically or chemically interact with drug substances either in solid state (Chen et al., 2005; Byrn et al., 2001; McDaid et al., 2003; Devi and Babu, 2000; Bruni et al., 2002; Dürig and Fassihi, 1993; Lessen and Zhao, 1996; Torres and Camacho, 1994) or liquid state (Ong et al., 1993; Chowhan and Chi, 1986a,b).

A common drug–excipient interaction is a charge interaction (Gordon et al., 1990; Crowley and Martini, 2001; Yamamoto, 1997). Excipients and drugs with ionizable groups, like carboxylic and amino groups, can generate anions or cations, respectively, depending upon the pH of the aqueous solution. When such an excipient is formulated with ionizable oppositely charged drug substance, an ionic association or interaction may occur between drug and excipient. In some cases, an interaction may lead to retention of drug in the excipient, which if insoluble may impact drug product analysis, such as solubility, disintegration, dissolution, and/or even bioavailability (Wang and Chowhan, 1990; Welling et al., 1982; Liabres, 1982; Akers, 2002; Hollenbeck, 1988). The degree of this impact depends on the physicochemical properties of the drug and excipient, the strength of the interaction and the ratio of the drug and excipient in formulations.

Metformin/Starlix® bilayer tablet is a new combination product for type II diabetes. The drug product contains two drug substances and excipients. During analytical method development and validation, the percent recovery of metformin was significantly lower than the theoretical values, especially, for solutions with low metformin concentration. This paper describes the approach to solve the metformin recovery issue.

2. Experimental

2.1. Chemicals

Metformin (*N*,*N*-dimethylimidodicarbonimidic diamide monohydrochloride) was obtained from Sandoz Pharmaceutical Corp. (Princeton, NJ, USA). Starlix® (*N*-(*trans*-isopropylcyclohexanecarbonyl)-D-phenylalanine) and bilayer

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tablets of metformin/Starlix® were obtained from Novartis Pharmaceuticals Corp. (East Hanover, NJ, USA). Arginine (TLC grade), lysine (TLC grade), glutamic acid (TLC grade), and histidine (TLC grade) were purchased from Sigma (St. Louis, MO, USA). Acetonitrile (HPLC grade), octane sulfonic acid sodium salt monohydrate (purity ≥ 97%), trifluoroacetic acid (HPLC grade), triethylamine (purity ≥ 99.5%), sodium dodecyl sulfate (purity ≥ 99%), sodium dihydrogen phosphate monohydrate (purity ≥ 98%), and phosphoric acid (85 wt.% solution) were purchased from Aldrich (Milwaukee, WI, USA). The following USP grade excipients, croscarmellose sodium, magnesium stearate, colloidal silica dioxide, and Avicel® were purchased from FMC Corp. (Phila, PA, USA), FACI SRL (Carasco GE, Italy), Cabot Corp. (Tuscola, IL, USA), and Quest International (Norwich, NY, USA), respectively. Povidone K30 and K90 were purchased from BASF AG (Ludwigshafen, Germany).

2.2. Sample preparation

The sample preparation solvent consisted of 50% acetonitrile and 50% water (v/v). One bilayer tablet dissolved in 50 ml of sample solvent was defined as 100% concentration of the sample solution, which contained 10 mg/ml of metformin, 2.4 mg/ml of Starlix® and 2.5 mg/ml of placebo. The placebo contained Povidone K90, magnesium stearate, Avicel®, Povidone K30, croscarmellose sodium, and colloidal silica dioxide. In method validation studies, the concentration of drug substances in sample solutions was varied from 0.05 to 1.0% in the low concentration range and from 20 to 100% in the high concentration range while the concentration of placebo was fixed at 2.5 mg/ml, which included 0.8 mg/ml of croscarmellose sodium. The sample solutions were further diluted by sample solvent after sonicating for 10 min and mechanically shaking for 30 min. The diluted solutions were analyzed by a high performance liquid chromatography method.

The stock solutions of arginine, lysine, glutamic acid and histidine for the competition screening test were 10 mg/ml each. For the competition mechanism studies, 0.302 mM of metformin and 0.302 mM of arginine were prepared separately in 50 ml volumetric flasks. Croscarmellose sodium was added into each of these solutions from 0 to 40 mg at 10 mg intervals and from 40 to 100 mg at 20 mg intervals. To investigate the influence of arginine concentration on metformin recovery, arginine was individually added from 0 to 70 mg at 10 mg intervals into 50 ml of 1 and 20% of metformin solutions.

The metformin/Starlix® bilayer tablet contains metformin, Povidone K90, and magnesium stearate in one layer and Starlix®, Avicel®, Povidone K30, croscarmellose sodium, colloidal silica dioxide, and magnesium stearate are present in the other layer.

2.3. HPLC and titration methods

Meformin, Starlix®, and arginine were analyzed by HPLC method, consisting of a Waters Alliance 2690 separation module and a reverse phase HPLC column (Xterra, RP18, 100 (L) × 3.9 mm (i.d.) with 3.5 μm particles). The peak intensities of metformin, Starlix® and arginine were measured using Waters model 996-PDA detector at a wavelength of 218 nm. The flow rate was 1.0 ml/min under ambient condition and the injection volume was 50 μl. Mobile phase A consisted of deionized water with 10 mM octane sulfonic acid sodium salt monohydrate adjusted at pH 2.7 with trifluoroacetic acid, and mobile phase B consisted of 80% acetonitrile and 20% 10 mM octane sulfonic acid sodium salt monohydrate adjusted at pH 2.7 with trifluoroacetic acid. Both mobile phases were degassed by vacuum before use. A 26 min linear gradient was used.

The number of moles of carboxylic groups (–COO^-) in croscarmellose sodium was determined by titration using a Brinkman 684 Titroprocessor. The titrants were 0.1000N of sodium hydroxide and 0.0997N of hydrogen chloride.

3. Results and discussion

3.1. Drug–excipient interaction

Metformin is a strong base whose pK_a is 12.4. This drug is easily protonated and carries a positively charged amino (=NH_2^+) group. Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. This excipient is insoluble in water, but can swell to two to four times of its original volume in water (Row et al., 2003). Because of the carboxylic groups, the surface of croscarmellose sodium is ionizable in an aqueous solution and carries a negatively charged ion (–COO^-) (Hollenbeck et al., 1983; Crowley and Martini, 2001). In the bilayer tablet, both metformin and croscarmellose sodium were in separate layers resulting in a minimal contact at the interface. Moreover, in the solid state the carboxylic group in croscarmellose sodium may not be dissociated due to low tablet water content of less than 2%. Hence, the drug–excipient charge interaction may be neglected. However, when the bilayer tablet was dissolved in the aqueous solution, the charge interaction between the positively charged metformin and the negatively charged croscarmellose sodium occurred. The interaction led to a fraction of metformin to be retained on the surface of croscarmellose sodium, leading to a 4–8% loss in metformin recovery from the tablets.

Table 1 shows the percent recovery of metformin and Starlix® in 0.05–1.0% and 20–100% concentration ranges of the theoretical concentrations of actives when these solutions were spiked with croscarmellose sodium based placebo. The recovery of Starlix® was between 87.2 and 97.6% in 0.5–1.0% range and between 99.6 and 101.8% in 20–100% range. The recovery of Starlix® in both ranges met the validation criteria, which were set as 80–120% in the 0.05–1.0% range, and 98–102% in the 20–100% range. In contrast, the percent recovery of metformin in both ranges failed the criteria due to the drug–excipient interaction. The recovery of metformin was found between 55.6 and 73.0% in the 0.05–1.0% range and between 91.9 and 98.0% in the 20–100% range as shown in Table 2. In the 0.05–1.0% concentration range, the recovery of metformin was much lower than its theoretical values. To increase the recovery of metformin, different compositions of extraction solutions were used according to the solubility of the bilayer tablet and chemical

Table 1
Percent recovery of metformin and Starlix® in different concentration solutions spiked with placebo

Percent concentration of drugs in solutions[a]	Percent recovery		Percent concentration of drugs solutions	Percent recovery	
	Starlix®	Metformin		Starlix®	Metformin
0.05	87.2	55.6	20	101.8	91.9
0.10	91.6	66.4	40	101.3	94.2
0.20	93.2	66.7	60	100.0	95.2
0.50	96.2	71.2	80	99.6	96.7
1.00	97.9	73.0	100	99.8	98.0

[a] Metformin and Starlix®.

Table 2
Percent recovery of metformin in different concentration solutions spiked with placebo with/without competition

Percent concentration of metformin in solutions	Percent recovery		Percent concentration of drugs in solutions	Percent recovery	
	Without arginine	With arginine		Without arginine	With arginine
0.05	55.6	107.6	20	91.9	98.7
0.10	66.4	104.4	40	94.2	98.7
0.20	66.7	98.7	60	95.2	99.2
0.50	71.2	106.4	80	96.7	99.4
1.00	73.0	102.0	100	98.0	99.1

Table 3
Percent recovery of metformin in the spiked sample solutions by different extraction solvents

Metformin in solution (%)	Sample extraction solvent	Recovery (%)
20	Water/acetonitrile (50%/50%)	91.9
20	Water/methanol (50%/50%)	93.9
20	10 mM sodium hydrogen phosphate solution at pH 2.5/acetonitrile (50%/50%)	92.1
20	10 mM SDS solution/acetonitrile (50%/50%)	91.9
20	10 mM OSAS solution at pH 6.8/acetonitrile (50%/50%)	92.4
20	20 mM OSAS solution at pH6.8/acetonitrile (50%/50%)	93.7
20	1% Triethylaminev solution/acetonitrile (50%/50%)	93.7

SDS, sodium dodecyl sulphate; OSAS, octane sulfonic acid sodium salt monohydrate.

properties of drug substances. Table 3 shows recovery of metformin by different extractions in the 20% concentration of metformin solutions. The low recovery of these extractions indicates existence of a strong interaction between the positively charged drug and the negatively charged excipient.

In the spiked solution, a possible structure for the metformin and croscarmellose sodium interaction may be a meta-stable six-member complex based on ion–dipole interaction and two $–O\cdots H–N^+$ hydrogen bonds (Kalinkova, 1999; Jackson et al., 2000). This complex might further be stabilized by the resonance structures as shown in Fig. 1a. The dynamic equilibrium of the charge interaction between metformin and croscarmellose sodium caused the drug recovery issue. The small amount of metformin lost in such drug–excipient interaction significantly affected the analytical method development and validation.

To solve the drug–excipient charge interaction, several approaches were tried. Due to the limits of solubility and stability of the drugs and excipients, only a competition method was chosen for the bilayer formulation. Based on pK_a and functional group, four basic amino acids (arginine, lysine, glutamic acid, and histidine) were initially selected for the competition screening test. When the same amount of the amino acids was added individually in the metformin sample solutions, these amino acids showed different competing capabilities. Table 4 shows the results of the screening test, in which 99.0% of metformin in the spiked solution was recovered by arginine competition. Compared to the arginine, the recovery of metformin by other amino acids was significantly less. Because of arginine's higher pK_a and similar interacting functional group of metformin, arginine demonstrated the highest capacity to displace metformin from the binding sites on croscarmellose sodium as shown Fig. 1b. One of the pK_as of arginine is 13.2[1], which is higher than that of metformin (pK_a = 12.4), and also higher than that of other amino acids.

3.2. Competitor–excipient interaction

As shown in Table 4, arginine is an ideal competitor for metformin compared with other amino acids. Based on the properties of arginine, arginine would be expected to interact with croscarmellose sodium with a greater affinity compared the interaction between metformin and croscarmellose sodium.

[1] From the Merck Index, 12th edition.

Table 4
Recovery comparison of metformin in the spiked sample solutions containing amino acids

Name of compound	Molecular formula	Highest pK_a	Percent metformin recovery[a]
Arginine	$H_2NC(=NH)NH(CH_2)_3CH(NH_2)CO_2H$	13.2	99.0
Lysine	$H_2N(CH_2)_4CH(NH_2)CO_2H$	10.3	96.5
Glutamic acid	$HO_2CCH_2CH_2CH(NH_2)CO_2H$	9.67	95.0
Histidine	$\overline{N=CHNHCH=C}CH_2CH(NH_2)CO_2H$	8.97	96.0

[a] The concentration of metformin, crosscarmellose and amino acid, is 2, 0.8, and 1 mg/ml, respectively.

Fig. 1b shows the possible competitor–excipient interaction in the solution or suspension.

To support our assumption of the competitor–excipient interaction, the relative binding constant of metformin and arginine with croscarmellose sodium were determined. For metformin–croscarmellose interaction, the drug–excipient interaction equation and equilibrium constant based on the interaction stoichiometry can be written as below:

$$[C^-] + [M^+] \leftrightarrows [CM] \quad (1)$$

$$K_{CM} = \frac{[CM]}{[C^-][M^+]} \quad (2)$$

where $[C^-]$ and $[M^+]$ represent the molar concentrations of the negatively charged croscarmellose sodium and positively charged metformin in the solution at equilibrium, respectively. [CM] represents the molar concentration of the metformin–croscarmellose complex at equilibrium. K_{CM} is an equilibrium constant of metformin–croscarmellose interaction.

Similarly for arginine–croscarmellose interaction, the competitor–excipient interaction equation and equilibrium constant can also be written as below:

$$[C^-] + [A^+] \leftrightarrows [CA] \quad (3)$$

$$K_{CA} = \frac{[CA]}{[C^-][A^+]} \quad (4)$$

where $[C^-]$ and $[A^+]$ represent the molar concentrations of the negatively charged croscarmellose sodium and positively charged arginine in the solution at equilibrium, respectively. [CA] represents the molar concentration of arginine–croscarmellose complex at equilibrium. K_{CA} is an equilibrium constant of arginine–croscarmellose interaction.

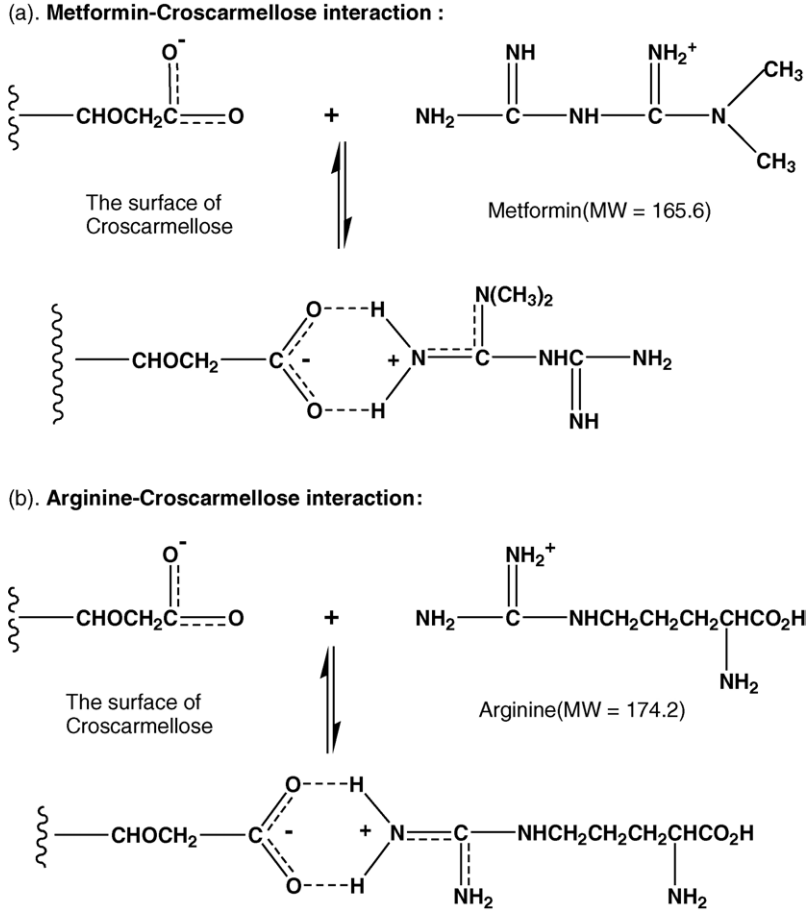

Fig. 1. Scheme of the possible charge interactions: (a) metformin–croscarmellose interaction; (b) arginine–croscarmellose interaction.

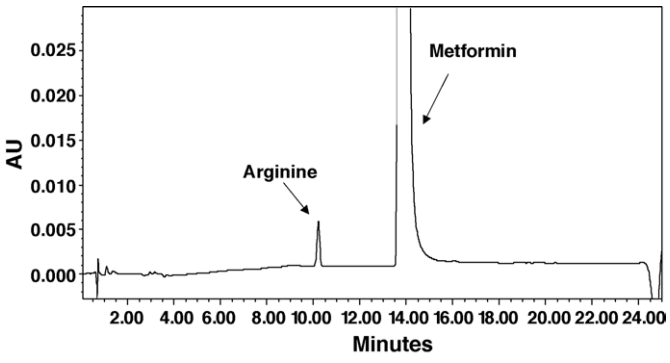

Fig. 2. A typical HPLC chromatogram of arginine and metformin in the solution.

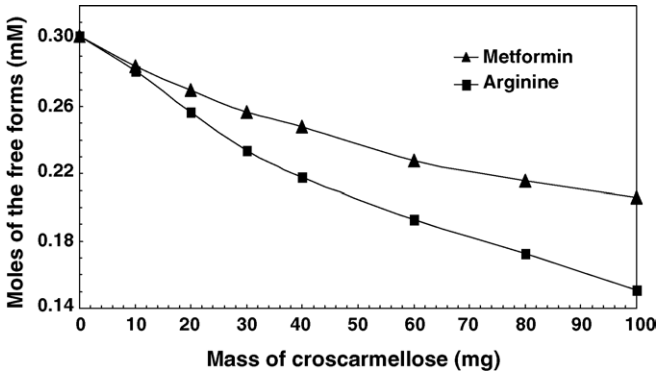

Fig. 3. Comparison of arginine–croscarmellose interaction to metformin–croscarmellose interaction in the suspensions.

By combining Eqs. (1) and (3), and (2) and (4), the competition equation and binding constants can be derived as follow:

$$[\mathrm{CM}] + [\mathrm{A}^+] \underset{K_1^{-1}}{\overset{K_1}{\rightleftarrows}} [\mathrm{CA}] + [\mathrm{M}^+] \tag{5}$$

$$K_1 = \frac{[\mathrm{CA}][\mathrm{M}^+]}{[\mathrm{CM}][\mathrm{A}^+]} = \frac{K_{\mathrm{CA}}}{K_{\mathrm{CM}}} \tag{6}$$

$$K_1{}^{-1} = \frac{[\mathrm{CM}][A^+]}{[\mathrm{CA}][M^+]} = \frac{K_{\mathrm{CM}}}{K_{\mathrm{CA}}} \tag{7}$$

K_1 is a binding constant, where arginine displaces metformin to form arginine–croscarmellose complex [CA]. K_1^{-1} is an opposite binding constant, where metformin displaces arginine to form metformin–croscarmellose complex [CM]. The direction of the competition depends on K_1 and K_1^{-1} values. In the competition, if $K_1 > K_1^{-1}$, the equilibrium of the competition will shift from the left side to the right side of Eq. (5) favoring the displacement of metformin. In contrast, if $K_1 < K_1^{-1}$, the equilibrium will shift from the right side to the left side. From further rearrangement, it is easy to derive that the K_1 is equal to $K_{\mathrm{CA}}/K_{\mathrm{CM}}$, and K_1^{-1} is equal to $K_{\mathrm{CM}}/K_{\mathrm{CA}}$.

To prove that arginine could displace metformin, an experiment was designed to determine the relative values of K_{CA} and K_{CM}. In the study, arginine and metformin solutions were individually spiked with different amounts of croscarmellose sodium. The initial amounts of metformin and arginine used in the solutions were the same. The amount of croscarmellose sodium spiked into metformin and arginine solutions were also the same. Since croscarmellose sodium was a crosslinked polymer and insoluble in aqueous solution, the weight concentration of croscarmellose sodium was used in the experiment rather than the molar concentration. After equilibration the spiked solutions were analyzed by a reverse phase HPLC method. The amounts of free metformin and free arginine in the solutions were monitored by their respective peak areas. The amount of metformin–croscarmellose complex and arginine–croscarmellose complex were indirectly determined by subtraction of free metformin and free arginine from their initial concentrations. Fig. 2 shows a typical chromatogram of arginine and metformin in the solutions, in which the peak of arginine eluted at retention time 10.2 min and the peak of metformin eluted at 13.9 min. The two peaks are well separated and can be quantitatively determined by external standard analysis.

As expected, when the same amounts of arginine and metformin in their solutions were spiked separately with croscarmellose sodium from 0 to 100 mg range, the amount of free arginine observed was much less than that of free metformin as shown in Fig. 3. In other words, the amount of arginine–croscarmellose complex formed was much higher than that of metformin–croscarmellose complex. For example, the amounts of arginine–croscarmellose complex and metformin–croscarmellose complex at 100 mg croscarmellose sodium solutions are 0.149 and 0.096 mM, respectively. As mentioned earlier, when the initial amount of croscarmellose sodium, $[\mathrm{C}^-]$, added in metformin solution and arginine solution are the same, and the initial concentrations of $[\mathrm{M}^+]$ and $[\mathrm{A}^+]$ are also equal, then [CA] > [CM] at equilibrium indicating that the equilibrium constant of arginine–croscarmellose (K_{CA}) is larger than that of metformin–croscarmellose (K_{CM}) in the charge interaction.

Since the concentration of carboxyl groups in croscarmellose sodium cancels in Eqs. (6) and (7), the amount of free arginine and free metformin in the solutions is enough to estimate the relative value of K_1 and K_1^{-1}. However, to quantitatively calculate K_1 and K_1^{-1}, a titrametric method was used to determine the moles of free carboxylic groups in a given amount of croscarmellose sodium. By an acid/base titration, 0.320 mM of the $-\mathrm{COO}^-$ group in 100 mg of croscarmellose sodium was found. After substituting the concentrations of $[\mathrm{C}^-]$, $[\mathrm{M}^+]$, $[\mathrm{A}^+]$, [CA], and [CM] into Eqs. (2) and (4), the equilibrium constants of K_{CA} and K_{CM} were obtained at the 100 mg of croscarmellose sodium suspensions. The equilibrium constant (K_{CA}) of arginine–croscarmellose interaction is 2.84×10^2 $[\mathrm{mol/l}]^{-1}$ and the equilibrium constant (K_{CM}) of metformin–croscarmellose interaction is 1.04×10^2 $[\mathrm{mol/l}]^{-1}$. Furthermore, the binding constants of K_1 and K_1^{-1} were determined at the 100 mg of croscarmellose sodium solution based on their relationship with K_{CA} and K_{CM}. The binding constant (K_1) of arginine–croscarmellose complex is 2.74 and the binding constant (K_1^{-1}) of metformin–croscarmellose complex is 0.36. The value of K_1 is almost 7.5 times larger than that of K_1^{-1}. The binding constants indicate that the charge interaction in the

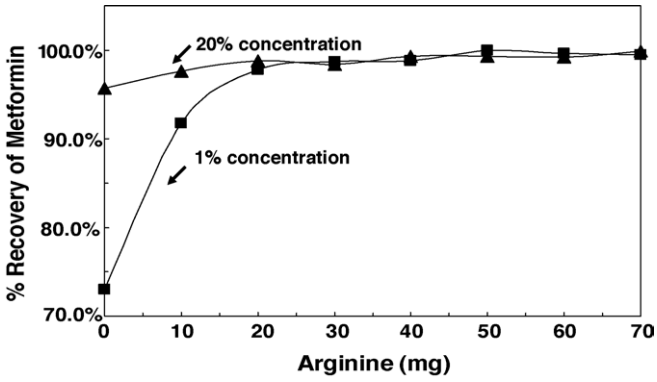

Fig. 4. Effect of arginine concentrations on the recovery of metformin in competition.

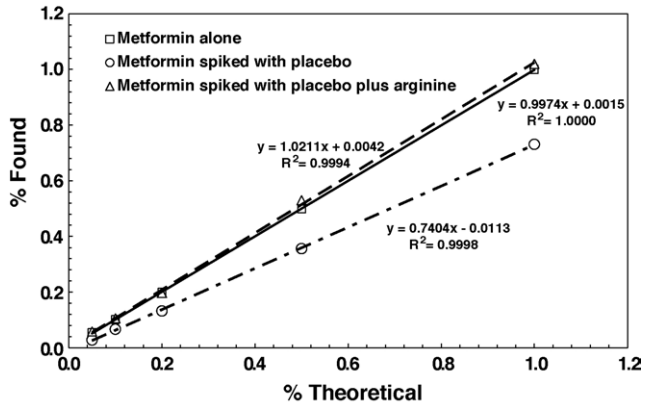

Fig. 5. The percent metformin found vs. the percentage of theoretical values: (1) metformin alone; (2) metformin spiked with placebo; (3) metformin spiked with placebo plus arginine.

competition is dominated by competitor–excipient interaction, not by drug–excipient interaction.

3.3. Competition by arginine

Based on the experimental results, arginine was selected as the competitor with metformin in the sample preparation. Fig. 4 shows the effect of arginine concentrations on the recovery of metformin at 1 and 20% concentration solutions spiked with croscarmellose sodium based placebo, when the amount of arginine was added from 0 to 70 mg at 10 mg intervals. The recovery of metformin significantly increased with increasing the amount of arginine up to 20 mg. After 30 mg the recovery of metformin reached a plateau. These curves indicate at least 30 mg of arginine is needed in the sample solution if the bilayer formulation contains 40 mg of croscarmellose sodium.

To eliminate the drug–excipient interaction in the method validation, 50 mg of arginine as per tablet was added to the sample solutions. Table 2 shows the recovery of metformin over a 0.05–1.0% concentration range with and without arginine competition. With arginine competition, the recovery of metformin dramatically increased to 102.0–107.6% range compared to the 51.5–73.1% range without arginine. Table 2 also shows the percent recovery of metformin in 20–100% concentration range with and without arginine competition. With arginine competition, the recovery of metformin significantly increased to 98.7–99.4% range compared to the 91.9–98.0% range without arginine. In the presence of arginine, the recovery of metformin in both of concentration ranges passed the validation criteria. On the other hand, arginine additive did not have any interference on the recovery of Starlix®.

Fig. 5 shows plots of the theoretical percent of metformin alone, metformin spiked with placebo, and metformin spiked with placebo and arginine versus their percent found in the range of 0.05–1.0%. The values of R^2 in these plots show that all these lines are linear. However, the slopes of these lines are not the same, 0.9974 for metformin alone, 0.7404 for metformin spiked with placebo, and 1.0211 for metformin spiked with placebo and arginine. The plot shows metformin spiked with placebo obviously deviated from that of metformin alone due to the drug–excipient interaction. The plot of metformin spiked with placebo and arginine is essentially superimposable with that of metformin alone due to the arginine competition.

4. Conclusion

The strong charged interaction between metformin and croscarmellose sodium was successfully eliminated by arginine competition. When a charge interaction between drug–excipient occurs in the aqueous solution, and negatively impacts on the recovery of drug substances, a competition method can be employed for elimination of the drug–excipient interaction. The pK_a and the functional group of the competitor are important considerations. In this example, arginine is an ideal competitor for the displacement of the charge interaction between drug–excipient due to its high pK_a value and the unique functional group. In this competition study, the binding constants of arginine–croscarmellose complex (K_1) and metformin–croscarmellose complex (K_1^{-1}) obtained from experiment data support the competition mechanism hypothesis. As a result, the percent recovery of metformin in presence of arginine was significantly increased to its theoretical values in both concentration ranges, especially in the 0.05–1.0% metformin concentration range.

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