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Is it the Method or the Process—Separating the Causes of Low Recovery

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ABSTRACT

During the development of a tablet formulation, a solvent capable of extracting 100% of the drug from the tablet excipients must be identified as part of the analytical assay method. When a low drug recovery from a tablet is observed with the assay method, it must be determined whether a problem with the manufacturing process exists, or if the extraction of the drug was incomplete. A solvent screen study was conducted with CP-122,721 prototype formulations to select a robust solvent for the assay method. However, low tablet assay values (ca. 95%) were routinely observed during tablet formulation development and process scale up. Drug-excipient interactions in a variety of solvents were subsequently evaluated to confirm the selection of the extraction solvent as capable of 100% extraction. At this point the focus of the investigation was placed on process-related sources of low recovery, such as loss of drug to manufacturing equipment and/or segregation during the tableting process. The results suggest that the low drug recovery observed for the CP-122,721 tablets was due to segregation during the manufacture, while the selected extraction solvent was able to eliminate any interactions between CP-122,721 and the tablet excipients.

Key Words: Drug excipient interactions; Microcrystalline cellulose; Croscarmellose sodium; Segregation.

INTRODUCTION

The development and process optimization of a tablet dosage form depends on a robust analytical method to provide accurate assay results for the formulation. One of the criteria for a reliable method is that it must provide a full recovery of the drug from the formulation matrix. The choice of extraction solvent is an essential part of the method development. Typically, a solvent screening process is carried out in

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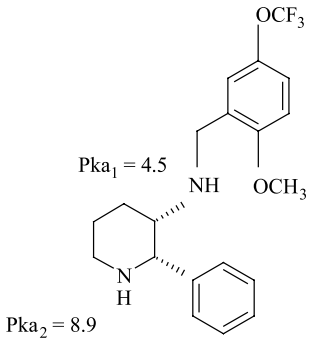

Figure 1. Chemical structure of CP-122,721.

which a series of solvents are evaluated by the drug recovery they can provide from the tablet.

During the early stages of the dosage form development, the manufacturing process has not been optimized. When incomplete recoveries are observed with the prototype formulations, it is difficult to confirm the feasibility of the chosen extraction solvent. Other factors that could contribute to the low drug recovery include the manufacturing process itself, or interactions between the drug and excipients in the extraction solvent.

The drug evaluated in this study was CP-122,721, a weakly basic drug with the structure presented in Fig. 1.

This compound has ca. 60 mg/mL aqueous solubility and >50 mg/mL solubility in methanol. Although a solvent screen was carried out with the prototype tablets as part of the method development process, low assay values (93–97% of label claim) were regularly observed for prototype tablets as well as tablets made at pilot and 10% commercial scales using the selected extraction solvent. These observations led to further investigations into drug/excipient interactions and the manufacturing process. A variety of CP-122,721 tablet samples were tested in order to identify whether the observed low drug recovery was related to a problem with the analytical assay method or a problem with the homogeneity of the tablet blend. The tablets used in this investigation included tablets manufactured at laboratory-scale and during process scale-up at a manufacturing facility. In addition, binary mixtures of drug substance with excipients were tested to gain an understanding of drug/excipient interactions.

MATERIALS AND METHODS

Materials

CP-122,721 drug substance and tablets were manufactured at Pfizer Global Research and Development (Groton, CT) or Pfizer Global Manufacturing (Freiburg, Germany). Excipients studied in this investigation included microcrystalline cellulose (Avicel PH200, FMC Biopolymer, Philadelphia, PA) and croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Philadelphia, PA) and mannitol (SPI Polyols, Inc., New Castle, DE). All other materials were of HPLC grade.

Analytical Methods

All tablets and drug/excipient mixture solutions were assayed by HPLC. Solutions were shaken on a reciprocating shaker at 225 oscillations per minute for 1, 2, or 3 hours and diluted to volume. Aliquots were centrifuged for 10–15 minutes and the supernatant transferred to HPLC vials. Isocratic HPLC on a Waters Puresil C18 column (4.6 mm i.d. $\times$ 150 mm, 5 μm particles) was used to analyze the solutions, using a mobile phase of 60% acetonitrile/40% 20 mM phosphate buffer with OSA and DTAP, a column temperature of 30°C and a 6 minute run time.

Extraction Solvent Development

A series of solvents, including water, 0.01 N HCl, 50/50 ACN/H_2O and 50/50 ACN/0.01 N HCl, were evaluated for extraction of CP-122,721 from the prototype tablets. Solutions were prepared to volume and shaken on a reciprocating shaker for 2 hours. Aliquots were pulled at several time points (10, 30, 45, 60, 120 minutes) in order to evaluate the kinetic behavior of the extraction.

Drug/Excipient Interaction Studies

Initial Assessment

Two excipients were investigated for potential drug/excipient interactions: microcrystalline cellulose (Avicel) and croscarmellose sodium (Ac-Di-Sol). Binary mixtures containing drug/Avicel and drug/Ac-Di-Sol were extracted with water. The amount of drug and excipient used was equivalent to the composition of a 10 mg tablet. Unless otherwise noted, these amounts were used for all of the binary solutions prepared in 50 mL flasks.

Effect of Ionic Strength

To determine the effect of ionic strength on the behavior observed for CP-122,721 with Avicel and Ac-Di-Sol, binary mixtures were assayed using aqueous solutions of varying ionic strength as the extraction

solvent. Extraction solvent pH was controlled at 6, with varying amounts of NaCl for an ionic strength control. Each solution was shaken for 3 hours prior to sampling for assay analysis.

Adsorption Isotherms

An adsorption isotherm was constructed by varying the amount of CP-122,721 and Ac-Di-Sol in a 0.001 M NaH_2PO_4 solution of pH 5.2. Solutions were prepared to cover a range of drug: Ac-Di-Sol ratios from 0.06:1 to 1.2:1. A similar experiment was conducted in which the ratio of CP-122,721 versus Avicel was varied from 0.00002:1 to 0.2:1 in a 0.001 M NaH_2PO_4 buffer solution at pH 5.2.

Effect of pH

Binary mixtures of CP-122,721 with Avicel and Ac-Di-Sol were prepared in a series of solutions with pH ranging between 3 and 8. The ionic strength was kept constant at $\mu=0.001$ using NaCl where necessary. This experiment was repeated using solutions of varying pH[1–12] at a constant ionic strength of $\mu=0.2$. NaH_2PO_4 and Na_2HPO_4 along with HCl and NaOH were used to vary the pH while maintaining constant ionic strength.

Effect of Addition of Acetonitrile

Acetonitrile was added to 0.01 N HCl in varying amounts (0–50% of extraction solvent) and these solutions were used as the extraction solvent for binary mixtures of drug with Avicel and Ac-Di-Sol.

Manufacturing Studies

Material Balance Experiment

To assess the possibility of drug adhering to the manufacturing equipment, two tablet manufacture runs were carried out at laboratory scale of 1 and 3 kg. The manufacturing equipment was rinsed after the completion of tablet compression runs. Tablet samples and rinse solutions were assayed.

Segregation Experiment

CP-122,721 prototype tablets (50 mg and 10 mg) were manufactured from a common blend with 50 mg tablets compressed first, followed by the 10 mg tablets. A second manufacture was carried out to produce three tablet lots at a 3 kg scale. Each batch of tablets was compressed from individual blend lots in the order of 10 mg tablets, followed by 50 mg, then 10 mg tablets. Tablet samples were taken at the beginning, middle, and end of each run and assayed.

Scale Up Manufacture

A scale up lot at a 120 kg scale was manufactured in a Pfizer commercial manufacturing site. Tablets were sampled over the course of the tablet compression run and assayed.

RESULTS AND DISCUSSION

Although CP-122,721 is highly soluble in water (ca. 60 mg/mL) and methanol (>50 mg/mL), none of the solvents evaluated during the solvent screen were able to provide 100% recovery after two hours of shaking. The highest recovery (~93%) was obtained with solutions of 0.01 N HCl, 50/50 ACN/0.01 N HCl and 50/50 ACN/H_2O (Fig. 2). Interestingly, with water as the extraction solvent, recovery reached 84% in 15 minutes with no increases with additional shaking up to 2 hours. Due to limited experience with this formulation, it was difficult to determine whether the ~93% recovery was due to inhomogeneous tablets or incomplete extraction. A mixture of 50/50 ACN/0.01 N HCl was chosen as the extraction solvent based on the recovery results and compatibility with mobile phase of the LC method.

To further evaluate the extraction efficiency of the selected solvent, two 50 mg tablets were made via ''direct compression.'' This involved placing known amounts of each excipient and drug substance into a tablet die, then compressing into a tablet, such that amounts of each tablet component could be accounted for within the tablet. In addition, a triturated mixture was prepared by adding each of the components (in the amount found in a 50 mg tablet) into a mortar and

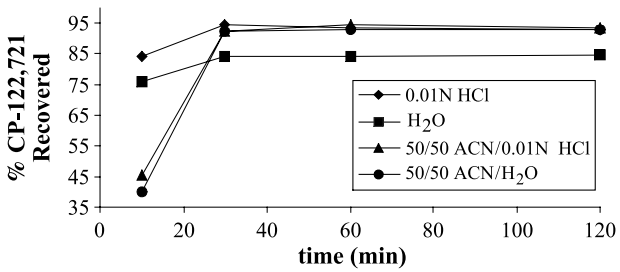

Figure 2. Kinetic data for four solvents from the initial solvent screen.

blending with a pestle to simulate the manufacturing process. Each of these samples was extracted with a solution of 50/50 ACN/0.01 N HCl. The average result for the directly compressed tablets was 101% LC, and the average for the triturated mixture was 99% LC. These results indicated that all of the drug was recovered from these samples. These results contrast with the low recovery (~93%) observed for the prototype tablets in Fig. 2.

In order to confirm the extraction capability of the chosen solvent, it was important to verify that no interactions between the drug and excipients were occurring in the solution. This type of interaction could potentially lead to a low free drug concentration in the assay solution. Interactions between weakly basic drugs and certain tablet excipients have been reported in the literature.[1–8] Therefore, investigations into potential interactions of CP-122,721 with excipients were conducted to assess the role of drug/excipient interactions in the low drug recovery observations.

Recovery of CP-122,721 from binary mixtures of drug and three major excipient components, microcrystalline cellulose, croscarmellose sodium, and mannitol, with water as extraction solvent are presented in Table 1.

Binary mixtures of drug with microcrystalline cellulose and croscarmellose sodium yielded less than 100% recovery. The interaction of CP-122,721 with croscarmellose sodium appeared stronger, as only 86% of the drug was recovered from this solution. This result was consistent with the tablet results obtained with water as the extraction solvent in the initial solvent screen (Fig. 2). Further interaction studies focused on microcrystalline cellulose (Avicel) and croscarmellose sodium (Ac-Di-Sol), both of which are insoluble tablet excipients.

As reported, interactions between weakly basic drugs with microcrystalline cellulose and croscarmellose sodium have been evaluated. These interactions were reported to be electrostatic attractions between the amine group(s) on the drug and the carboxylic acid groups on the excipients. Studies carried out on binary

Table 1. CP-122,721 recovery from binary mixture of drug and major excipients.

Component	% Drug recovery
CP-122,721, chloride salt	–
Microcrystalline cellulose	97%
Mannitol	100%
Croscarmellose sodium	86%

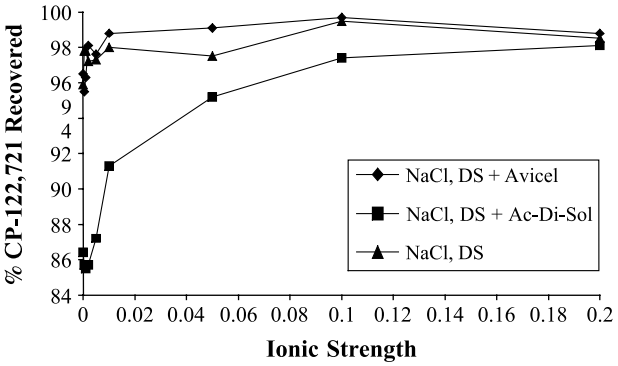

Figure 3. % CP-122,721 recovered vs. ionic strength.

mixtures of the CP-122,721 and excipients in aqueous extraction solvents of varying ionic strength (controlled with NaCl) confirmed this as a possible mechanism for an interaction between CP-122,721 and these two excipients (Figs. 3 and 4).

As illustrated in Fig. 3, drug recovery from Avicel was 96–99%, indicating no drug loss in binary mixtures of CP-122,721 and Avicel in solutions with ionic strength (μ) controlled with NaCl between 0.01–0.2. This indicated no apparent interaction between CP-122,721 and Avicel. However, an interaction was observed in solutions that contained Ac-Di-Sol and drug at $\mu < 0.1$ (86–96% recovery). This interaction was reduced with increasing ionic strength until $\mu = 0.1$, at which point the interaction appeared to be eliminated.

These results suggested that the interaction observed here was an electrostatic attraction between the amine groups on CP-122,721 and the carboxylic acid groups on the Ac-Di-Sol. This interaction resulted in the CP-122,721 adsorbing onto the insoluble excipient. The decrease in adsorption with increasing ionic

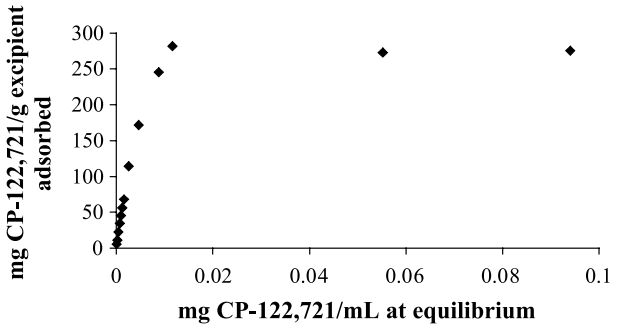

Figure 4. mg drug/g excipient adsorbed vs. mg drug/mL at equilibrium.

strength was due to competition of the Na^+ cation for the adsorption sites.[2]

As a final confirmation of the adsorptive behavior of CP-122,721 onto Ac-Di-Sol, an adsorption isotherm was constructed by varying the amount of CP-122,721 and Ac-Di-Sol in a 0.001 M NaH_2PO_4 buffer solution of pH 5.2. Solutions were prepared to cover a range of CP-122,721: Ac-Di-Sol ratios of 0.06:1 to 1.2:1.

The level of adsorption, measured as mg CP-122,721/g excipient vs. CP-122,721 concentration, is plotted in Fig. 4. Adsorption increased with the concentration of CP-122,721 relative to a constant amount of Ac-Di-Sol at pH 5.2. Maximum adsorption of ca. 280 mg CP-122,721/g Ac-Di-Sol was reached when the ratio of total drug to Ac-Di-Sol was 0.4:1. At this point the adsorption leveled off. This behavior indicated that the data followed the Langmuir adsorption model. The Langmuir adsorption model describes monolayer coverage of an adsorbed species on a limited number of adsorption sites on a solid. In this model, a plateau was reached when the maximum amount of the species that can be adsorbed at these sites was reached, which was observed in Fig. 4. A Langmuir plot of the data (Fig. 5) indicated a good linear fit to the model.

No adsorption was observed in any of the solutions with CP-122,721: Avicel ratios ranging from 0.00002:1 to 0.2:1. Even in mixtures in which Avicel was in great excess compared to the drug, no adsorption occurred.

As stated earlier, these data collectively demonstrated an interaction of CP-122,721 with Ac-Di-Sol but not with Avicel. The interactions between a Parke-Davis compound (CI-977) containing two tertiary amine groups with both Ac-Di-Sol and Avicel have been reported in the literature. The interaction was attributed to adsorption of the drug onto both Ac-Di-Sol and Avicel in purified water.[3] This experiment utilized Avicel PH102, which has a particle size of 90 microns. Our experiment involved the use of Avicel

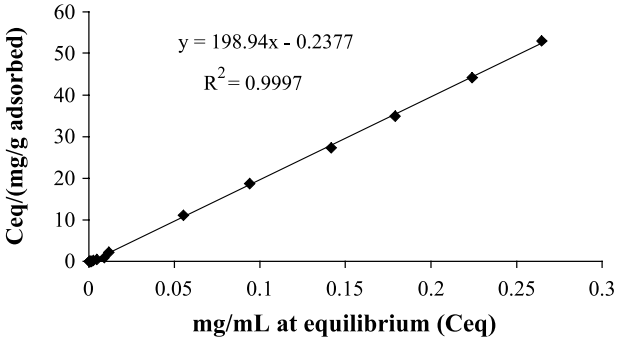

Figure 5. Langmuir adsorption isotherm of CP-122,721 onto Ac-Di-Sol.

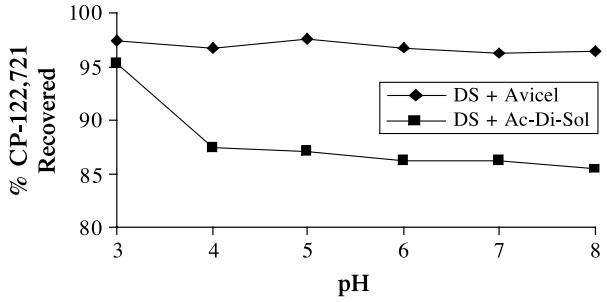

Figure 6. % CP-122,721 recovered vs. pH, μ=0.001.

PH200 with a particle size of 180 microns. Observation of less adsorption to larger particles has been observed[9,10] and explained as being due to reduced surface area as compared to an equivalent amount of smaller particles. A good deal of research has been carried out to investigate the differences in degree of adsorption with different Avicel manufactures,[3,4,7–13] indicating that this type of interaction could vary with the Avicel batch used in the tablet manufacture.

An increase in interaction with increasing drug: Avicel ratio was also reported for Merck compound MK-329, which contains two tertiary and two secondary amines.[1] However, no interaction between CP-122,721 and Avicel was observed in our experiment over a wide range of ratios. In contrast, even with drug in excess of Ac-Di-Sol, a strong interaction was observed in our experiments.

As the interaction between basic amine groups and acidic carboxyl groups was identified as the electrostatic attraction, an investigation of this mechanism in solutions of varying pH was conducted. Under these conditions, the drug-excipient interaction between CP-122,721 and Ac-Di-Sol was strongest at higher pH, and decreased slightly with decreasing pH until pH=4 (Fig. 6). At this point, the drug recovery rose from

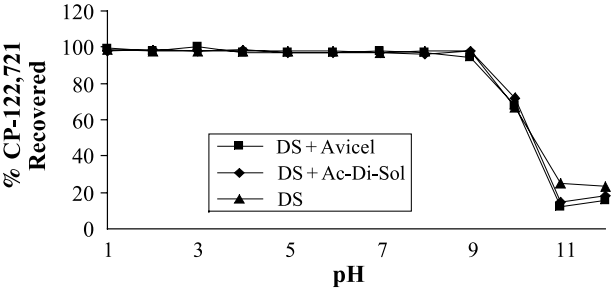

Figure 7. % CP-122,721 recovered vs. pH, μ=0.2.

~88% at pH=4 to ~95% at pH=3. No interaction between the drug and Avicel was observed.

This data confirmed the electrostatic interaction between CP-122,721 and Ac-Di-Sol. The trend observed here has been reported in the literature for weakly basic drugs and croscarmellose sodium, as carboxylic acid groups have a pKa of around 4.[6] At pH>4, these groups are negatively charged. With a pK_{a1} of 4.5 and a pK_{a2} of 8.9, CP-122,721 is positively charged up to pH~9. Ac-Di-Sol would therefore attract the positively charged amine groups on the drug between pH 4–9.

When the ionic strength was held at 0.2, ~100% recovery was achieved for all three solutions until pH=9 (Fig. 7). At pH >9, % recovery dropped off to ~25% for DS alone and ~18% for DS with Avicel and with Ac-Di-Sol. The loss of recovery at pH >9 was due to the decrease in drug solubility rather than adsorption, as evidenced by the decreased recovery with DS alone. The pK_a for CP-122,721 is 8.9, so it is in neutral form at pH >9 with low aqueous solubility.

Comparing Figs. 6 and 7, it was clear that the pH effect observed at μ=0.001 was not present at μ=0.2. The effect of ionic strength on the drug-excipient interaction was much stronger than the pH effect. Figure 7 indicates that the high concentration of sodium cations at 0.2 M, more than 400 times greater than the concentration of DS in solution, was competitively binding to these negatively charged sites on Ac-Di-Sol and eliminating the electrostatic interaction with the drug.

The effect of adding an organic component to the extraction solvent was studied as another approach to eliminate the interaction. As stated earlier, the extraction solvent chosen for these tablets was 50/50 ACN/0.01 N HCl (Fig. 8). Percent recovery of CP-122,721 was in the range of 100% to 102%. These results indicated that an aqueous solution of 0.01 N HCl provided 100% drug recovery in the presence of both excipients. The addition of acetonitrile at different

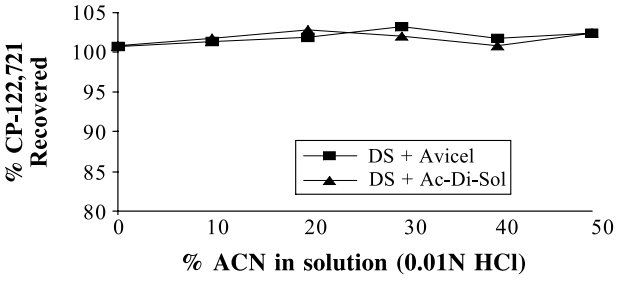

Figure 8. % CP-122,721 recovered vs. % ACN in 0.01 N HCl solution.

Table 2. Results from mass balance experiments.

Blend	Tablet assay (average)	Rinse assay
1 kg	97%	3%
3 kg	99%	1%

levels to the 0.01 N HCl also allowed 100% recovery of the drug. Any drug/excipient interaction was eliminated in all of the samples tested. Based on these results, it was clear that the selected extraction solvent of 50/50 ACN/0.01 N HCl was able to fully extract CP-122,721 from the formulation matrix.

These extraction study results combined with the early prototype tablet results indicated that the low recovery values (~93%) seen for the prototype tablets were most likely due to a problem with tablet homogeneity. Thus, subsequent investigations focused on characteristics of the manufacturing process.

In a material balance experiment, 100% recovery was achieved when including results from the rinse samples (Table 2).

The drug loss to equipment was ca. 1% after correcting for the blend size, which would not fully account for the low assay results obtained with prototype tablets. In addition, drug loss on equipment would become negligible during scale up manufacture with increases in volume-to-surface ratio. Potency results from an early prototype tablet compression run also indicated that drug loss to the manufacturing equipment might be occurring. In this trial, the compression order was 50 mg tablets followed by 10 mg tablets. The results showed that assay values for the 50 mg tablets (94–95% LC) were consistently lower than those (97–101% LC) for the 10 mg tablets. Because the tablets compressed first showed lower potency, it appeared that drug loss to the manufacturing equipment could be the cause, as was indicated earlier in Table 2. It was hypothesized that the drug could be adhering to the surfaces of the manufacturing equipment early in the run. At some point, the surfaces would become saturated, and there would be no further drug loss later in the run.

To test this hypothesis, an additional three lots of tablets were manufactured. The compression trial was conducted in the order of 10 mg tablets compressed first, followed by 50 mg, and then the 10 mg tablets. Each tablet lot was made from a common blend of 3 kg. Tablets from the beginning, middle, and end of each tablet compression run were assayed (Fig. 9).

In this study, tablet assay results within each run showed a consistent increase from the beginning to the

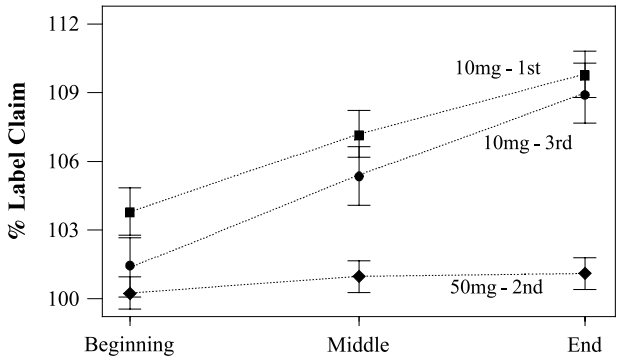

Figure 9. Results of drug segregation/saturation on manufacturing equipment study.

end of run. Assay results for the two 10 mg tablet sets increased from 101% to 110% LC over the course of the run, while the assay data for the 50 mg tablet trial ranged from 100% to 101%. These changes indicated blend segregation was occurring over the course of the run. In addition, the assay value increase was much more pronounced for two trials of 10 mg tablets than that of 50 mg tablets, since the compression time for the 10 mg tablets was five times longer than the time required for the 50 mg tablets. Therefore, the blend remained in the hopper five times longer for the 10 mg tablet manufactures. As the blend segregation was occurring as a function of time, the change in assay values was minimum for the 50 mg tablets.

Moreover, all of the 10 mg tablets in this study were found to have assay values of greater than 100% label claim. The reason for this was not clear. In any case, these results indicated that segregation was likely having a larger effect on tablet potency than any drug potentially adhering to the manufacturing equipment.

During the tablet manufacture, a robust blend without segregation would result in tablets of consistent assay values throughout the compression trial, whereas blend segregation would result in changes in tablet assay values. Segregation can occur in blends of non-identical solid particles due to differences in density, shape, surface properties and size of the particles.[11–15] Much work is done during the development of a tablet formulation to overcome these differences and provide a homogeneous tablet blend. Granulation samples are taken from various points in the blender and assayed in order to confirm the drug content before tablets are pressed. However, between the blender and the tablet press, movement of the tablet blend can lead to segregation during the tableting process. The segregation can be profiled as a function of time by stratified sampling over the course of the tableting process.

Results from a scale-up manufacture of 120 kg scale again showed low average potency. The average result from the content uniformity testing was 97.3% LC with a range of 94.3–99.0% LC. Tablets were sampled periodically during the tablet compression run and assayed (Fig. 10).

Tablet potency was low (88%) for the first tablets off the press, then leveled off at ~97% and showed an upward trend (101%) at the end of the tablet compression run. The higher potency at the end of the run pointed to segregation[15] rather than DS loss to equipment.

A potential mechanism for segregation during the scale up manufacture was fluidization occurring during the material transfer. During the manufacture, blend was charged into a hopper located on the next floor with a ~8 feet drop. Up-flowing air carried solids upward. Fine particles in the blend would fall back slower than the heavy particles, which resulted in blend segregation. Sieve analysis of the blend samples showed that the fine particles were drug rich, thus tablets made near the end of the run contain more drug and have higher assay values than the tablets collected at the beginning. Moreover, several kg of blend remained in the hopper after the compression trial. This material was not sampled for testing. However, based on the fluidization model, this portion of the blend would be expected to be drug rich and have higher assay values, which would contribute to overall mass balance of the batch. This behavior was reported for a tablet manufacturing case study[6] in which high tablet assay values were observed at the end of a tablet compression run. The blend was subsequently discharged from the blender into drums. Material sampled from the top of the drum gave assay results of over 120%.

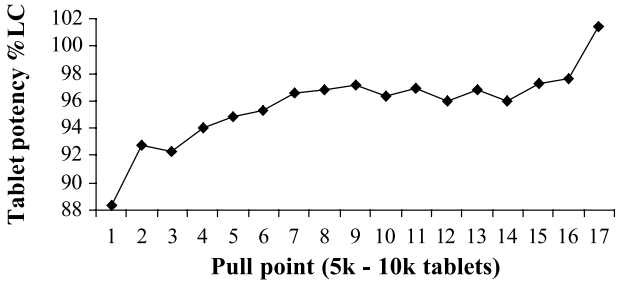

Figure 10. Assay results for stratified sampling of tablets during manufacture.

As discussed above, drug adhesion to manufacturing equipment would result in initial low tablet potency, which would increase until reaching a plateau. However, drug segregation by fluidization during the tablet compression process would result in a continuing increase in tablet potency, as that observed in Fig. 10. The profiles observed at both laboratory (Fig. 9) and manufacture (Fig. 10) scales confirmed occurrence of blend segregation during tablet compression. Therefore, it was concluded that blend segregation was the cause of the generally low and variable potency values observed for CP-122, 721 tablets.

CONCLUSION

The study demonstrated the selected extraction solvent (50/50 ACN/0.01 N HCl) was feasible for extracting CP-122,721 from tablet matrix. A significant interaction between croscarmellose sodium (Ac-Di-Sol) and CP-122,721 was observed in aqueous solution. The interaction was caused by CP-122,721 adsorbing onto croscarmellose sodium, which occurred in aqueous solutions of low ionic strength between pH 4–9. This adsorption was determined to be due to an electrostatic interaction between the amine groups on the drug and carboxylic acid groups on the excipient. In solutions with either pH<3 or an ionic strength >0.05 M, this interaction was eliminated. The extraction solvent used for the CP-122,721 assay method, 50/50 ACN/0.01 N HCl, was confirmed to be capable of 100% drug extraction.

Assays of tablet blends and tablets made at laboratory and manufacture scales led to the conclusion that segregation of the blend during the tablet manufacturing process was occurring at both small and large-scale manufactures. The segregation occurring during the large-scale manufacture followed a fluidization model.

The combination of these results led to the conclusion that an average of 93% recovery of drug from prototype tablets and 97% from the large-scale manufacture tablets was an accurate measure of tablet potency. The low potency of the tablets was due to segregation during the tablet manufacture.

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