Chapter 2
Drug Excipient Interactions

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Abstract Unintended physicochemical interaction of an excipient with a drug substance in a dosage form can result in the complexation or binding of the drug, resulting in slow and/or incomplete drug release in a dissolution medium. It is important to assess the risk whether such interactions would reduce oral bioavailability of a drug from its dosage form. This chapter describes the development of a methodology to assess the biorelevance of the drug release impact of drug-excipient binding interactions using a model compound, brivanib alaninate. This methodology was developed using a combination of modeling and simulation tools as well as experimental data generated *in vitro* and *in vivo*. In addition, general application of this principle and methodology to other drug substances and binding affinities of drugs with excipients as a function of dose is described.

Keywords Adsorption · Bioavailability · Binding · Brivanib alaninate · Croscarmellose sodium · Excipient · Isothermal titration calorimetry · Langmuir adsorption isotherm · Wet granulation

Abbreviations

AUC_{0-t}	Area under the plasma concentration-time curve from dosing till time of last sampling (72 h)
BA	Brivanib alaninate

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CCS	Croscarmellose sodium
C_{max}	Maximum concentration reached in plasma
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methyl cellulose
ITC	Isothermal titration calorimetry
NMR	Nuclear magnetic resonance
SSG	Sodium starch glycollate
$t_{½}$	Plasma half life
T_{max}	The time of maximum plasma concentration
USNF	United States National Formulary
V_d	Volume of distribution
xPVP	Crospovidone

2.1 Introduction

The selection of excipients is vital in the design of a quality drug product. Excipients and their concentration in a formulation are selected based not only on their functionality but also on the compatibility between the drug and excipients (Narang et al. 2009). An incompatibility may be defined as an undesirable drug interaction with one or more components of a formulation resulting in changes in physical, chemical, microbiological, or therapeutic properties of the dosage form (Narang et al. 2009). The potential existence of such incompatibilities in a drug product, or in a mixture of the drug substance with one or more excipients is investigated using excipient compatibility studies. These studies also provide justification for selection of excipients and their concentrations in the formulation as required in regulatory filings (Narang et al. 2009).

Compatibility studies are usually aimed at identifying the most common or previously encountered incompatibilities. For example, an incompatibility in dosage form can be identified as any of the following changes: change in color/appearance, loss in mechanical properties (e.g., tablet hardness), changes to dissolution performance, physical form conversion, loss through sublimation, a decrease in potency, and increase in degradation products (Narang et al. 2009). The compatibility studies can be carried out in several different modalities with an aim to study the impact of various environmental factors and process parameters, in addition to product composition (Fig. 2.1; Narang et al. 2009). Certain aspects of drug-excipient interactions, such as unintended drug-excipient binding, are usually not studied in an excipient compatibility study. This chapter highlights the importance of such interactions and discusses methodologies that can be utilized to study their potential impact on oral bioavailability of a drug.

Unintended physicochemical interaction of an excipient with a drug substance in a dosage form can result in the complexation or binding of the drug, resulting in slow and/or incomplete drug release in a dissolution medium. It is important to assess the risk whether such interactions would reduce the bioavailability of a drug

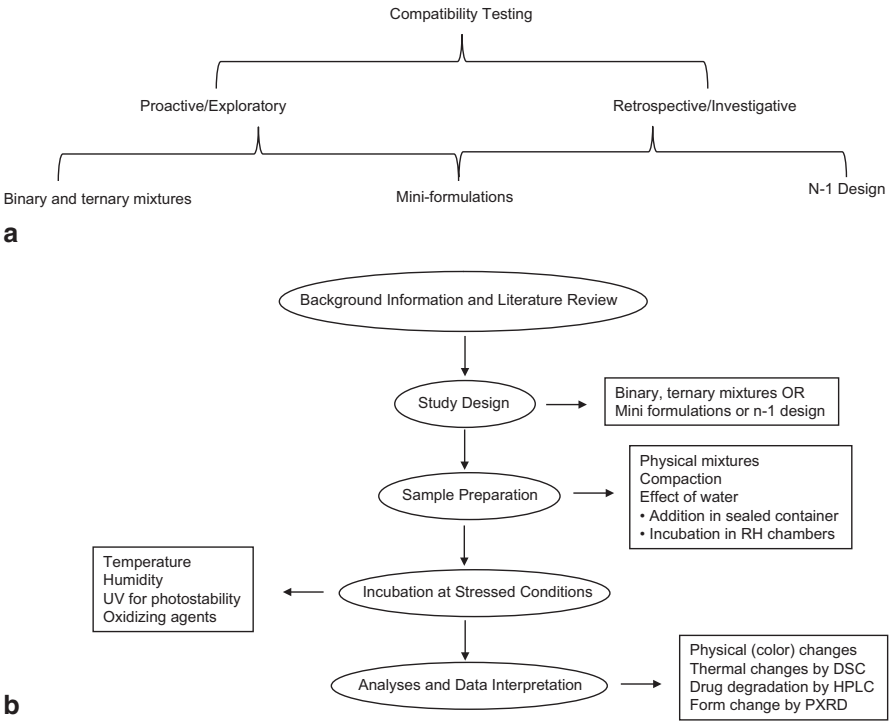

Fig. 2.1 Typical modalities of *compatibility testing* (**a**) and the study execution (**b**). Various stages of the compatibility testing are highlighted in *ovals* and the key decisions and variables involved in each stage are mentioned in *square boxes*. Reproduced with permission from (Narang et al. 2009)

from its dosage form. This chapter describes the development of a methodology to assess the biorelevance of the drug release impact of drug-excipient binding interactions using a model compound, brivanib alaninate. This methodology was developed using a combination of modeling and simulation tools as well as experimental data generated *in vitro* and *in vivo*. In addition, general application of this principle and methodology to other drug substances and binding affinities of drugs with excipients as a function of dose is described.

Drug-excipient binding interaction in the dosage form can affect *in vitro* drug release (Balasubramaniam et al. 2008; Huang et al. 2006). For example, Huang et al. reported a strong ionic interaction between metformin and croscarmellose sodium (CCS; Huang et al. 2006). This interaction caused the entrapment of metformin in the croscarmellose sodium matrix, leading to low analytical recovery. It was overcome by the use of arginine, a stronger binding competitor, indicating that the interaction was ionic and reversible. Chien et al. reported the binding of oxymorphone derivatives with CCS and sodium starch glycolate (SSG) in water as a function of solution pH and analyzed the data using Freundlich adsorption principles (Chien et al. 1981). Hollenbeck reported the pH-dependence of chlorpheniramine interaction with CCS (Hollenbeck et al. 1983). The author later reported the effect

of phenylpropanolamine hydrochloride-CCS interaction on the drug's *in vitro* dissolution and *in vivo* exposure (Hollenbeck 1988). In this study, three lactose-based formulations were tested, containing either no disintegrant, or 10% w/w starch or CCS as a disintegrant. Although an *in vitro* dissolution test in water showed significant (40%) drug binding to CCS, no significant differences were observed among the three formulations in the cumulative amount of drug excreted in the urine of 6 healthy human subjects over a period of 24 h after a single oral dose. The authors, however, did not discuss the reason for lack of *in vivo* effect of drug-excipient binding interaction observed *in vitro*.

Literature suggests that drug-excipient binding interaction in the dosage form that affect a drug's *in vitro* release may or may not affect a drug's oral bioavailability. For example, increase in drug dissolution by complexation with cyclodextrin corresponded with increased oral bioavailability of griseofulvin (Dhanaraju et al. 1998) and spironolactone (Kaukonen et al. 1998); but not of naproxen (Otero-Espinar et al. 1991) and tolbutamide (Kedzierewicz et al. 1993). Also, reduction in dissolution by complexation of halofantrine with magnesium carbonate (Aideloje et al. 1998) and of tetracycline with magnesium aluminum silicate (Veegum; Healy et al. 1997) corresponded with their reduced oral bioavailability; but not for the complexation of phenylpropanolamine with croscarmellose sodium (Hollenbeck 1988).

Ionic drug-excipient binding interactions are most commonly encountered in the use of ion exchange resins, such as sulfonated and/or carboxylated polystyrene backbone for binding basic drugs, for controlled/sustained drug delivery (Mahore et al. 2010). For example, complexation of dextromethorphan (Jeong and Park 2008) and phenylpropanolamine (Raghunathan et al. 1981) with ion exchange resins reduces drug release that corresponds with altered oral bioavailability. Whether a release-modifying drug-excipient interaction results in altered oral bioavailability of a drug is conventionally determined on a case-by-case basis.

A guidance on whether drug-excipient binding interaction in an oral dosage form poses risk of low bioavailability of the drug is generally lacking in literature. Fransen et al. studied the interaction between three commonly used superdisintegrants and several drugs with different physicochemical properties. In addition to the ionic interactions between cationic drugs and anionic polyelectrolyte disintegrants, such as CCS and sodium starch glycollate, the authors postulated that amphiphilic drugs could interact with superdisintegrants to a greater extent than simply by ion exchange due to greater entropic gain caused by the aggregation of surfactant inside the polyelectrolyte (Fransen et al. 2008). In such cases, the interaction may not be overcome by increasing the ionic strength of the dissolution medium. Nevertheless, ionic interactions could be disrupted in the presence of physiological salt concentration in the dissolution medium, which was considered as an indication of potential lack of biorelevance of such interactions (Fransen et al. 2008). Thus, this study emphasized the importance of the strength of interaction, which was assessed by the reversibility of interaction at physiologically relevant salt concentration—a criterion that was also considered an indication of biorelevance of the interaction.

We addressed the question whether a drug-excipient binding interaction in the dosage form would affect a drug's oral bioavailability. Most basic amine drugs that are substantially ionized and soluble at the same pH as an insoluble excipient of opposite charge are likely to undergo such interactions. Prior literature suggests that an ionic binding interaction that is overcome with the use of physiological salt concentration is unlikely to reduce a drug's oral bioavailability. However, there is no guidance in literature regarding the drugs whose interaction may not be overcome by physiological salt concentration. Using an example of one such drug-excipient interaction, we probed whether *in vitro* techniques such as Langmuir binding isotherm and isothermal titration calorimetry (ITC) to assess the extent and strength of an interaction are able to indicate *in vivo* relevance of such an interaction. Our studies indicated that reversible and pH-dependent drug-excipient binding that is weaker than a drug-drug self-association does not affect oral bioavailability of high dose drugs. In addition, we developed a direct and objective measure of strength of drug-excipient interaction in the solution state, since drug gets absorbed from the solution state. We propose the use of ITC to assess the relative strength of drug-excipient and drug's self-association binding interactions.

The interaction of a model hydrophobic (log $P = 2.5$), weakly basic ($pKa = 6.9$), amine drug, brivanib alaninate (abbreviated, BA; Huynh et al. 2008), with the salt of a weakly acidic ($pKa = 4.8$) polymeric excipient, croscarmellose sodium (CCS), was investigated by dissolution studies. Strength of BA-CCS interaction was assessed by Langmuir adsorption modeling and ITC. Non-biorelevance of BA-CCS interaction was predicted using oral drug absorption modeling and confirmed by an oral drug pharmacokinetic study in monkeys.

2.2 Materials and Methods

Microcrystalline cellulose and croscarmellose sodium were procured from FMC Biopolymer (Philadelphia, PA); hydroxypropyl cellulose from Aqualon (Wilmington, DE); crospovidone from BASF Corporation (Florham Park, NJ); colloidal silicon dioxide from Cabot Corporation—Becca Golden (Alpharetta, GA); and magnesium stearate from Mallinckrodt, Inc. (St. Louis, MO). A model amine drug, brivanib alaninate (abbreviated, BA), was obtained from Bristol-Myers Squibb, Co. (New Brunswick, NJ). Sodium acetate, potassium phosphate, Triton X-100, sodium taurocholate, and all other reagents were procured from Sigma-Aldrich, Inc. (St. Louis, MO).

2.2.1 Tablet Manufacturing

An immediate release oral tablet formulation containing BA was manufactured by a wet granulation process using conventional excipients. Briefly, BA was mixed with intra-granular disintegrant (CCS or crospovidone), binder, and filler in a Diosna

high shear mixer (Diosna Bierks & Sohne GmbH, Osnabrück, Germany), followed by granulation with water. The granules were sized using Comil (Quadro Engineering Corp., Waterloo, ON, Canada) and blended with extra-granular excipients in a bin blender (A&M Process Equipment Ltd., Toronto, ON, Canada). Tablets were compressed on a Korsch press (PH106, 6-stations, Korsch Maschinenfabrik, Berlin, Germany) at target 800 mg press weight and 28 strong cobb unit hardness. Tablets were coated with 15% w/w a hydroxypropyl methylcellulose (HPMC)-based coating suspension (Opadry®, Colorcon, Inc., Harleysville, PA) in a Vector LDCS Hi-Coater® (Vector Corporation, Marion, IA) using standard operating parameters.

2.2.2 Drug Release Studies

In vitro drug release of 400 mg strength BA tablets was studied at pH 1.2, 4.5, and 6.8, using 1000 mL of an aqueous medium in compendial (United States Pharmacopeia) dissolution Apparatus 2 (paddle) at 75 rpm and 37 °C. Dissolution was carried out in 0.1 N HCl (pH 1.2), 22 mM sodium acetate buffer (pH 4.5), and 50 mM potassium phosphate buffer (pH 6.8) containing 1% w/v Triton X-100. In addition, to assess the strength of binding, dissolution in pH 4.5 acetate buffer was carried out at higher buffer concentrations (66, 170, 250 mM). A 10 mL sample was collected at 5, 10, 15, 20, 30, 45, and 60 min and replaced with a fresh medium equilibrated to 37 °C. At 60 min, the paddle speed was increased to 200 rpm. Dissolution was continued until 90 min, at which point a final 10 mL sample was collected. All the samples were diluted appropriately and analyzed for drug content using a validated high performance liquid chromatography (HPLC) method.

2.2.3 BA-CCS Binding Study

Binding of BA to CCS was studied in 105 mM acetate buffer with 45 mM sodium chloride at different drug/excipient molar ratios. Briefly, CCS was dispersed in the buffer in a beaker using a magnetic stirrer at different concentrations, followed by the addition of BA at 4.5 mM concentration, and equilibration at room temperature for 4 h. Then, the solution was filtered through 0.45 µm pore diameter polytetrafluoro ethylene (Teflon) syringe filter, followed by HPLC analysis for BA content. In some studies, sodium taurocholate was dissolved in the buffer solution at different concentrations before the addition of BA and CCS.

2.2.4 Modeling and Simulation

CCS is a hydrophilic polymeric excipient that forms an insoluble colloidal dispersion in the aqueous medium. Isothermal adsorption of a solute (BA) in the solution phase on the solid substrate (CCS) is represented as,

$$\mathrm{BA+CCS} \rightleftharpoons \mathrm{BA\text{-}CCS}$$

The association (binding) equilibrium constant, b, is given by,

$$b = \frac{[BA-CCS]}{[BA][CCS]} \tag{2.1}$$

The dissociation equilibrium constant, k, is given by the inverse,

$$k = \frac{[BA][CCS]}{[BA-CCS]} \tag{2.2}$$

This binding was modeled by Langmuir isotherm.

$$y = y_m\left(\frac{bc}{1+bc}\right) \tag{2.3}$$

where y is the amount of BA (in mmole) adsorbed on one mmole of CCS, y_m, is the maximum adsorption capacity of BA on CCS (mmole BA/mmole CCS), c is the concentration of free BA in solution (in mM), and b represents the association (binding) equilibrium constant (mM^{-1}).

Rearranging,

$$\frac{c}{y} = \frac{1}{y_m b} + \frac{c}{y_m} \tag{2.4}$$

Thus, a plot of c/y against c gives a straight line, from which y_m and b can be estimated.

The effect of drug-excipient binding on oral drug absorption was estimated by simultaneously solving the equations for free drug concentration in the gut and the drug absorption, as described below. The resulting plasma drug concentrations were estimated using the drug's pharmacokinetic parameters in a two compartmental model. Thus, amount of drug absorbed into the plasma (central compartment, or compartment 1; Fig. 2.2) is given by,

$$\frac{dXA}{dt} = k_a \times XC \tag{2.5}$$

where XA is the amount of drug absorbed, dXA/dt is the rate of drug absorption per unit time t, k_a is the absorption rate constant, and XC is the amount of free drug available in the gut.

Amount of free drug in the gut (XC) is given by,

$$XC = X - XA - XY \tag{2.6}$$

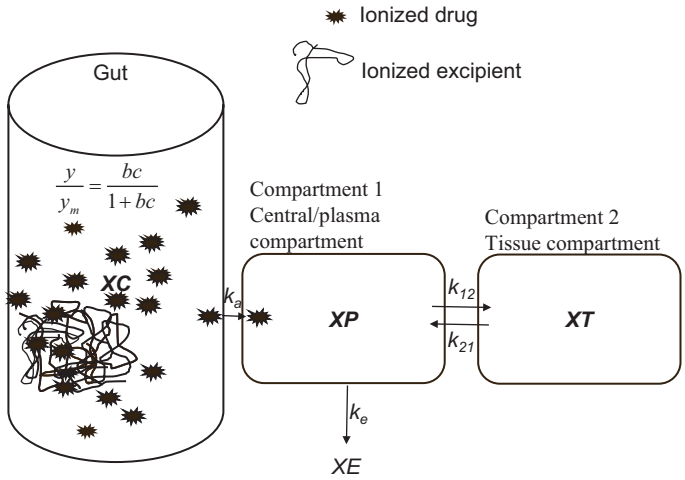

Fig. 2.2 Schematic of a model for assessing the effect of drug-excipient binding interaction on oral absorption and plasma pharmacokinetics. Reproduced with permission from (Narang et al. 2012)

where *X* is the administered dose, *XA* is the amount absorbed, and *XY* is the amount of drug bound to CCS—which is estimated using the Langmuir isotherm.

In addition, if a drug's pharmacokinetic profile is defined by a two-compartmental model, drug concentration in the plasma and the tissue compartment can be obtained by,

$$\frac{dXP}{dt} = k_a \times XC - k_{12} \times XP - k_e \times XP + k_{21} \times XT \tag{2.7}$$

$$\frac{dXT}{dt} = k_{12} \times XP - k_{21} \times XT \tag{2.8}$$

$$\frac{dXE}{dt} = k_e \times XP \tag{2.9}$$

where *XP* is the amount of drug in plasma, *XE* is the amount of drug eliminated from the plasma compartment, k_{12} is the rate of drug transport from compartment 1 (central or plasma) to compartment 2 (tissue), k_{21} is the rate of drug transport from compartment 2 to compartment 1, k_e is the elimination rate constant from the central compartment, and *XT* is the amount of drug in the tissue compartment.

Simultaneously solving these equations estimates amount of free drug in the gut, amount of drug absorbed, and the plasma drug concentration as a function of time (Fig. 2.2). This model allows parameter sensitivity analysis using a range of biopharmaceutical and pharmacokinetic parameters to identify cases where drug-excipient interaction may or may not pose significant bioavailability risk. For example, the effect of drug-excipient binding interaction on the plasma concentration-time profile

can vary significantly depending on drug's dose, and absorption rate constant. Numerical solution of the equations shown above was carried out using Scientist 3.0 software (Micromath Research, St. Louis, MO).

2.2.5 Isothermal Titration Calorimetry (ITC)

Thermal changes associated with BA-CCS binding interaction were studied by ITC using iTC-200 (Microcal—GE Healthcare, Piscataway, NJ). Briefly, 200 µL of CCS solution at 0, 1, 3, 9, 20, 30, 40, 50, 60, 70, 85, or 100 mM concentration in 50 mM pH 4.5 acetate buffer was loaded in the cell and 35 µL of 10 mM BA solution in the same buffer was loaded in the syringe. Titration was carried out at 25 °C by making 20 injections of 2.5 µL every 180 s at a rate of 30 µL/min, while mixing the contents in the cell using the in-built paddle at 1000 rpm. Enthalpy change associated with each injection was recorded. ITC data was analyzed using Microcal-Origin 7.0383 software (OriginLab Corporation, Northampton, MA).

2.2.6 Animal Pharmacokinetic Study

A two-way crossover pharmacokinetic study was carried out between tablets manufactured with or without CCS in healthy male cynomolgus monkeys after a single oral dose of 400 mg. Eight monkeys with body weights ranging from 3.18–4.94 kg were dosed with 400 mg tablets. A 7-day washout period was observed between crossover dosing. Blood samples were collected for up to 72 h postdose. BA concentration in plasma was determined using a validated liquid chromatography followed by tandem mass spectroscopy method. The animal study was carried out at WuXi AppTec, Suzhou, Jiangsu Province 215004, China with approval of the institutional animal care and use committee under the study #BMS-20090417 obtained in April, 2009.

2.2.7 Statistical Methods

Statistical analysis of significance of differences in drug release rates in different dissolution media (Fig. 2.3a) was carried out by analysis of variance (ANOVA) and for the effect of formulation on drug release from two formulations (Fig. 2.3b) by unpaired two-tailed t-test, after confirming the assumption of equal variances by the F-test, at $\alpha = 0.05$ for all time points (JMP 8.0, SAS Institute, Inc., Cary, NC). The dissolution profiles did not meet the requirements for comparison by the similarity factor (Moore and Flanner 1996). Pharmacokinetic parameters from the animal study were determined by non-compartmental analysis using WinNonlin v5.2 (Pharsight Corporation, Mountain View, CA). A bioequivalence analysis between

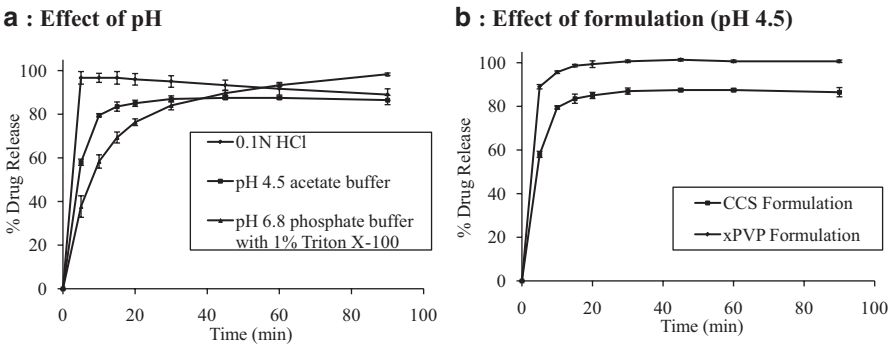

Fig. 2.3 Drug release studies. Comparison of drug release from a BA formulation containing *CCS* (**a**) in different pH media, and (**b**) with a formulation not containing *CCS* in *pH 4.5* acetate buffer. The data plotted is the average ± standard deviation of $n = 3$ tablets. In comparison of the effect of different pH media (Fig. 2.2a), data in the three pH media at all time points (except 60 min) were statistically significantly different. In comparison of the effect of formulation (Fig. 2.2b), data from the two formulations was statistically significantly different at all time points. Reproduced with permission from (Narang et al. 2012)

the two profiles was conducted by calculating the 90% confidence interval for the ratio of log-transformed pharmacokinetic parameters C_{max}, T_{max}, and AUC_{0-t}. The plasma concentrations between the two groups were compared at each time point by repeated measures ANOVA at $\alpha = 0.05$.

2.3 Results

2.3.1 BA-CCS Binding in Tablets

Dissolution studies on a tablet formulation containing 400 mg of BA and 24 mg of CCS (BA/CCS m/m ratio = 9.8) showed incomplete (~80%) drug release in pH 4.5 acetate buffer, although nearly complete release was obtained in 0.1 N HCl and pH 6.8 phosphate buffer with 1% w/w Triton X-100 (Fig. 2.3a). Complete drug release in 0.1 N HCl was followed by decrease in drug concentration due to degradation at highly acidic pH (data not shown). On the other hand, drug release studies at pH 6.8 required the addition of a surfactant to generate sink conditions in the dissolution vessel, since drug solubility at this pH is extremely low (<10 μg/mL). The intermediate pH of 4.5 offers both adequate solubility and stability of BA. Thus, sink condition is present in the dissolution vessel at pH 4.5 and incomplete drug release at this pH was not a result of the dissolution method. Also, pH 4.5 falls within the range where both BA and CCS are substantially ionized (discussed later).

When drug release from a formulation with CCS was compared with another formulation with crospovidone (xPVP) as a non-ionizable intra-granular disintegrant

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