International Journal of Pharmaceutics 514 (2016) 364–373

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pre-absorption physicochemical compatibility assessment of 8-drug metabolic cocktail

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ARTICLE INFO

Article history:
Received 26 March 2016
Received in revised form 4 June 2016
Accepted 8 June 2016
Available online 9 June 2016

Chemical compounds studied in this article:
Metoprolol (PubChem CID: 11957594)
Caffeine (PubChem CID: 2519)
Midazolam (PubChem CID: 4192)
Pravastatin (PubChem CID: 16759173)
Flurbiprofen (PubChem CID: 3394)
Omeprazole (PubChem CID: 4594)
Digoxin (PubChem CID: 2724385)
Montelukast (PubChem CID: 5281040)

Keywords:
Metabolic cocktail
Co-administration
Physicochemical interaction

ABSTRACT

A comprehensive 8-drug metabolic cocktail was designed to simultaneously target 6 Cytochrome P450 enzymes and 2 membrane transporters. This study aimed to assess the pre-absorption risk of this new metabolic cocktail which contained metoprolol, caffeine, midazolam, pravastatin, flurbiprofen, omeprazole, digoxin and montelukast. This paper describes a systematic approach to understand whether the co-administration of the 8 selected drug products, i.e., the physical mixing of these products in the human gastro-intestinal environment, will create any issue that may interfere with the individual drug dissolution which in turns modify the total amount or timing of their availability for absorption. The evaluation consisted of two steps. An initial evaluation was based on theoretical understanding of the physicochemical properties of the drugs and the gastro intestinal environment, followed by in vitro dissolution tests. The results indicated that the designer 8-drug cocktail has acceptable pre-absorption compatibility when dosed simultaneously, and recommended the progression of the cocktail into clinical validation study.

1. Introduction

Pharmaceutical dosage forms are packages of active pharmaceutical ingredients (APIs) and excipients. Excipients are added for various desired functionalities of the dosage forms, including manufacturability, bioavailability modification and ease of user administration. Since excipients are in intimate contact with APIs, there are potential risks of chemical and/or physical interactions between the excipients and the APIs which could lead to undesired outcomes, including API degradation, dosage form performance alternation, or formation of potentially toxic degradants. This understanding is the basis of pharmaceutical formulation development and therefore suitable excipients are usually carefully screened and selected by formulators based on the specific requirements for each dosage form.

Commonly used pharmaceutical excipients are normally relatively pharmacologically inert and chemically stable. However, some of these excipients have functional groups that can interact with some APIs. For example, reducing sugars (glucose and lactose) can cause a Maillard reaction (Bharate et al., 2010), which commonly described as a browning reaction, with an amino functional group. An experienced formulator will avoid using reducing sugars containing excipients when formulating a drug with an amine functional group. Furthermore, excipients are not neatly pure, based on the origin of the starting materials and manufacturing process, it may contain impurities, even though at trace amount quantity, which can initiate and propagate undesired interactions. For example, formaldehyde residue in polyethylene glycol 300 and polysorbate 80 has been found to be the cause of drug oxidation (Nassar et al., 2004). As a result, the required purity and grade of the excipients are usually tightly controlled by the drug manufacturers. The formulation development process became significantly more complicated when more than one API, such as fixed dose combination products, are involved because

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http://dx.doi.org/10.1016/j.ijpharm.2016.06.028
0378-5173/

drugs are designed to be pharmacologically active and can contain relatively active functional groups. Drug-drug interaction (DDI) should be strictly avoided to maintain the stability and potency of the drugs.

Physicochemical incompatibility can also occur when multiple dosage forms are administered together because each of the dosage forms is designed separately. Orally administered dosage forms are carefully designed and formulated in such a way that the APIs are dissolved and therefore available for absorption at the site of absorption, i.e., the targeted portion of the gastrointestinal tract, at the appropriate rate. The occurrence of chemical or physical interactions among any of the ingredients in the dosage forms involved, such as complexation, binding or precipitation, can interfere with drug dissolution, which in turns changes the total amount or timing of dissolved free drug availability for absorption and therefore impact the drug bioavailability profiles.

Broadly speaking, there are two types of risks that may impact bioavailability when multiple dosage forms are co-administered orally: 1) Pre-absorption risks – These are potential chemical or physical interactions between the ingredients (drugs and excipients) among the dosage forms as described above, and also the influence of a drug or excipients on physiological pH which in turn interferes with the dissolution of a second drug prior to absorption; 2) Post-absorption risks – These are potential pharmacokinetics drug–drug interactions cause by competing metabolic enzymes or cell membrane transporters. Cytochrome P450 (CYP) enzymes are the major enzymes in drug metabolism accounting for about 75% of the total drug metabolism (Guengerich, 2008). Certain drugs can also induce or inhibit CYP enzymes, or alter the active secretion of renal tubules, and therefore influence the drug clearance of other drugs indirectly. Both pre-absorption and post absorption risks increase as higher number of dosage forms are co-administered.

When a drug is supplied to a patient within a mixture, there is a potential of physicochemical interactions (i.e., pre-absorption risk) that may interfere with drug available for absorption. For example, the stability of commonly used drugs with enteral nutrient formulas (ENFs) was studied to ensure the suitability of using these drugs for patients on ENFs. The reported methods for determining the physical compatibility of drugs with ENFs include the observation/determination of viscosity change, particle growth, granulation, precipitation, phase separation, pH and osmolarity change, and concentration analysis (Strom and Miller, 1990; Klang et al., 2013; Cutie et al., 1983; Holtz et al., 1987; Burns et al., 1988; Crowther et al., 1995). It has reported that some drugs formed a solid mass immediately in the test tube with ENF (Klang et al., 2013), this reaction could have caused the obstruction of a feeding tube. Based on *in vitro* experiment, Holtz et al. could not recommend the addition of methyldopa, theophylline or phenytoin in suspension to the ENFs studied (Holtz et al., 1987). A clinical study in 1989 showed a decrease in bioavailability of about 10% and lower maximum serum concentration in volunteers administered carbamazepine suspension with an ENF (Bass et al., 1989). Similarly, compatibility of intravenous medications (Knudsen et al., 2014) during co-administration with parenteral nutrition (Bouchoud et al., 2013) have also been studied to ensure compatibility of the mixtures.

CYP enzymes can reduce or alter the pharmacologic activity of many drugs and facilitates their elimination (Wilkinson, 2005). Many factors, including genetics, dietary, medications, and disease state, can influence the activity or expression of these enzymes (Zanger and Schwab, 2013) and the marked inter-subject variability of the individual CYP enzymes have been clinically observed (Zanger and Schwab, 2013). The CYP polymorphism in human population has been shown to be a major contributor to inter-subject differences in drug response including side effects (Wilkinson, 2005; McGraw and Waller, 2012). Consequently, the involvement of CYP enzymes and their polymorphism are usually well studied during the drug development process today. The knowledge provides useful insight for patient population selection as well as predicting potential clinically significant drug–drug interactions that may occur with other drugs. Membrane transporters can also be major determinants of the pharmacokinetic, safety and efficacy profiles of drugs (Giacomini et al., 2010). Clinical pharmacokinetic drug–drug interaction studies have suggested that transporters often work together with drug-metabolizing enzymes impacting drug absorption and/or elimination (Giacomini et al., 2010; Zhou et al., 2013).

Today a standard clinical approach for investigating potential pharmacokinetic related drug–drug interaction is by co-administrating the molecule of interest with a metabolic probe. A metabolic probe is a drug known to mainly metabolize by a specific CYP enzyme. The same practice is applicable to membrane transporters. Since there are multiple CYP enzymes and transporters that could interfere with drug distribution and metabolism, it can be a highly resource intensive exercise to investigate these potential interactions separately in clinical studies. As a result, the idea of administrating a metabolic probe cocktail, which is the simultaneous administration of multiple metabolic probes, was born. Several metabolic probe cocktails have been reported in the literature: e.gs. Cooperstown cocktail (Streetman et al., 2000; Chainuvati et al., 2003), Cologne cocktail (Wyen et al., 2008), Pittsburg cocktail (Frye et al., 1997; Zgheib et al., 2006), Inje cocktail, and Basel cocktail (Donzelli et al., 2014).

There are 2 basic requirements of a practical metabolic probe cocktail: 1) from the absorption, distribution, metabolism and excretion (ADME) perspective, these probes should not significantly influence each other, and 2) there are no significant adverse reactions when the probes are co-dosed. Unexpected adverse effects from cocktail studies have been reported (Pedersen et al., 2013). There are advantages and disadvantages to each of the published metabolic cocktails, but the main drawback is they do not comprehensively cover all of the more common CYPs and transporters that are known to cause clinical drug–drug interactions. With the intention to create a better and more comprehensive drug cocktail, the authors' set off to design an 8-probe metabolic cocktail that includes probes for major CYP enzymes (CYP 1A2, CYP2C19, CYP2D6, CYP2C8, CYP2C9, CYP3A) and transporters (P-glycoprotein and OATP). The basic steps of design, testing, and validation of the 8-drug metabolic cocktail's effort are described below. Some steps took a few iterations.

1. Select key probe drugs and corresponding analytes, including metabolites, for the intended targets.
2. Examine the potential pharmacokinetic interactions of pre-selected probe combination, using simulation software, and their potential pharmacodynamic interaction by understanding the class of compound into which each substrate belonged, literature research, and detailed review of their product labels.
3. Assess the pre-absorption physicochemical related risks of pre-selected probe combination in their intended clinical dosage forms.
4. Validate the concept via a clinical trial.

The prediction of potential pharmacokinetic interactions of the cocktail in step 2 was conducted using Simcyp software (Simcyp, Certara, Saint Louis, MO). At the time the study was conducted, the software allowed a maximal of 4 CYP compounds to be simulated simultaneously. Multiple combinations of 4 CYP compounds were simulated and no significant interactions were predicted. Based on FDA DDI decision trees, the authors did not anticipate potential OATP DDI within the substrate combination. Although P-gp