Review Article

Food-Drug Interaction

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Pharmacokinetic food–drug interactions

With increasing generic substitution, food–drug interaction studies have gained considerable importance. Food–drug interaction studies focus on the effect of food on the release and absorption of a drug. In view of dramatic and clinically relevant food effects observed with certain theophylline sustained release formulations (Hendeles *et al*., 1985; Karim *et al*., 1985a, b; Smolensky *et al*., 1987), bioequivalence between a Test and a Reference formulation under only one nutritional condition, e.g. fasting, is by no means sufficient to allow generic substitution (Blume *et al.,* 1991). The reported food effects, with *AUC* increases of 100 % and decreases of 50 % for certain formulations (Karim *et al.,* 1985 a, b), are far beyond the usually accepted 25 % increase and 20 % decrease in bioequivalence studies between formulations. The CPMP (2001) guidance on bioequivalence also addresses this issue with particular emphasis on controlled release formulations. The FDA (2002) guidance recommends a study comparing the bioavailability under fasting and fed conditions for all orally administered modified release drug products. Modified release formulations include two essentially different types of release modifications, so-called **'prolonged release'** formulations and **'delayed release'** formulations.

Classification of food effects

Early characterization of food effect response is important in drug development to provide dosing conditions that will minimize variability in drug absorption during pivotal clinical trials. Food effect studies are also important in testing *in vivo* performance of a dosage form under widely different physiological conditions.

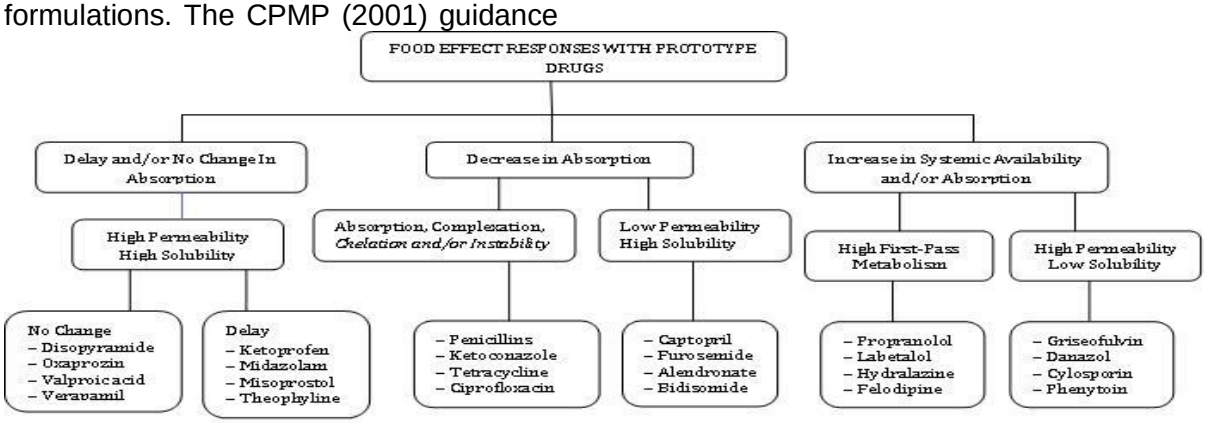

Fig.1: Classification of the food effect responses of prototype drugs on the basis of: (i) stability, chelation and/or complexation; (ii) effect on metabolism, and (iii) effect on permeability and/or solubility (Karim *et al.,* 1996).

The various ways in which food can effect gastrointestinal (GI) physiology, and thereby drug absorption, are summarized in Figure: 1 (Karim *et al.,* 1996). Of great importance for the drug absorption process are changes in gastric emptying time, GI motility, splanchnic blood flow, and GI secretion.

The absorption of drugs from the gastro-intestinal tract can be affected considerably by simultaneous intake of meals, particularly meals with a high fat content. In this regard the following factors play an important role: increase in pH in the stomach, intensification of bile secretion, reinforcement of motility, increase of blood-flow and retardation of the gastric transit time. Prior to initiating an *in vivo* food–drug interaction study, some of these factors should be mimicked *in vitro*. Ideally, the *in vitro* release should not be affected by pH value, buffer capacity, surface tension, turbulence of the dissolution medium and agitation by the apparatus. The most recent regulatory requirements on *in vitro* dissolution can be found in the corresponding guidelines. A comprehensive overview of the various *in vitro* dissolution tests together with rather extensive examples was presented by Dietrich *et al*., 1988. The absence of all of the above mentioned *in vitro* factors on the dissolution of the formulation investigated was confirmed *in vivo* by extensive food–drug interaction studies which clearly demonstrated lack of food interaction for this formulation (Schulz *et al*., 1987; Steinijans and Sauter *et al.,* 1993).

On the other hand, the ability of the *in vivo* equivalence methodology to detect major *in vitro* modifications was convincingly demonstrated by Steinijans *et al*. (1995). Differences were seen in the *in vivo* pharmacokinetic characteristics for two apparently identical theophylline sustained release products, which were used as reference products in bioequivalence studies in the US and in Europe, respectively. Although both reference formulations were manufactured by the same international group according to the same *in vitro* controlled release principle, their *in vivo* differences in concentration-time profiles could – in this case retrospectively – be explained by different *in vitro* dissolution profiles after 4 hours.

The relevance of a pH-dependency on the *in vitro* dissolution and hence on the *in vivo* bioavailability has been known for a long time, even dramatic effects in the case of some sustained release formulations (Hendeles *et al*., 1985; Karim *et al*., 1985b). However, pH dependency still is a cause of significant food interactions with certain marketed modified release formulations (Wonnemann *et al*., 2006).

Experimental design of food–drug interaction studies

As drug intake with or after meals is quite common, by Blume *et al.,* 1991 had already suggested the following scheme of bioequivalence studies in the case of controlled release formulations (cf. Figure 1).

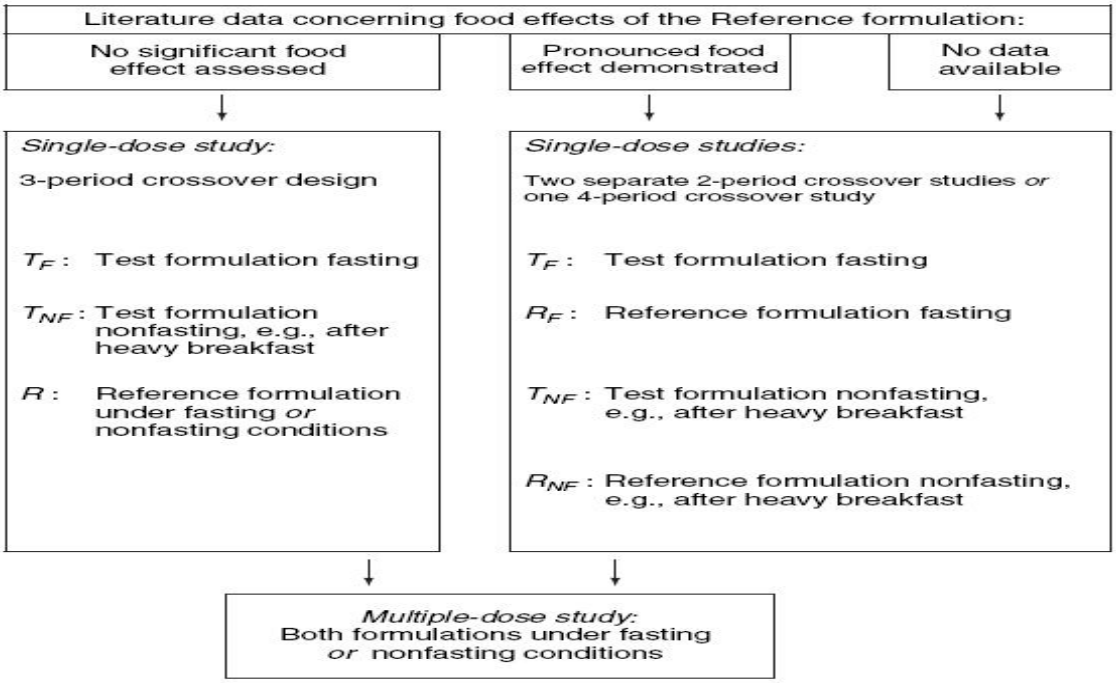

Fig. 2: Scheme of studies proposed to assess bioequivalence of controlled release dosage forms (with the permission of Professor Henning Blume).

There are no universally accepted standards of meal composition. Detailed information on the composition of a high fat American breakfast can be found in the excellent overview by Karim *et al.,* 1996; further information addressing the composition of breakfast, lunch and evening meals can be found in Steinijans and Sauter *et al.,* 1993. Similarly to 'lack of drug–drug interaction' as discussed in the previous chapter, 'lack of food–drug interaction' can also be handled as an equivalence problem utilizing the well-established methodology (Schulz *et al*., 1987; Steinijans and Sauter *et al.,* 1993; CPMP, 2001; FDA, 2002). If 'lack of food–drug effect' cannot be demonstrated, the resulting food.

Example: Theophylline food interaction study

The following example from the work of Steinijans and Sauter *et al.,* 1993 illustrates the obvious food–drug interaction with one formulation, whereas the other formulation appears to be free of any relevant food effect (upper panel). Effects (point estimate and 90 % confidence limits), together with the recommended mode of administration, should be clearly stated in the labeling of the particular formulation.

Table I: Summary of some significant Food-Drug Interactions

Drugs (Category)	Food	Drug-Food Interaction
Acarbose, mercaptopurine	at start of each meal Cow's milk **(Nekvindova J, *et al.,* 2007)**	maximum effectiveness reduce bioavailability
Ace inhibitors	Empty stomach	absorption is increased
Acetaminophen	Pectin	delays its absorption and onset
Antibiotics	with milk products **(Ayo JA *et al.,* 2005)**	that complex with some antibiotics and prevent their absorption. reduced bioavailability
Ca^{+2} channel	Grape fruit juice	increases the bioavailability
Celiprolol	Orange juice	the intestinal absorption is inhibited
Cimetidine, rupatadine	with food(any type)	increase bioavailability
Cycloserine	High fat meals	decrease the serum concentration
Esomeprazole	High-fat meal	bioavailability was reduced
Glimepiride	with breakfast	absolute bioavailability
Glimepiride	with breakfast	absolute bioavailability

Isoniazide	Plants medicinal herbsoleanolic acid	exerts synergistic effect
Levothyroxine	Grapefruit juice	delay the absorption **(Hansten PD *et al.*, 2004)**
Monoamnine Oxidases	Tyramine-containing food (**Frankel EH. *et al.*, 2003).**	hypertensive crisis
Nsaids	Alcohol	can increase risk of liver damage or stomach bleeding Beverages the c max and auc0-alpha significantly increased **(Schmidt LE *et al.*, 2002)**
Propranolol	Rich protein food	serum level may be increased
Tamoxifen	Sesame seeds	negatively interferes with Tamoxifen in inducing regression of established mcf-7 tumor size but beneficially interacts with Tamoxifen on bone in ovariectomized athymic mice
Theophyline	High-fat meal & grape fruit juice Caffeine	increase bioavailability increases the risk of drug toxicity
Warfarin	High-protein diet Vegetables containing vitamin k Charbroiled Cooked onions Cranberry juice Leafy green vegetables Charbroiled	Raise serum albumin levels, decrease in international normalized ratio (INR) Interferes with the effectiveness & safety of warfarin therapy. decrease warfarin activity increase warfarin activity elevated INR without bleeding in elderly patient thromboembolic complications may develop decrease warfarin activity

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