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Ethanol−Drug Absorption Interaction: Potential for a Significant Effect on the Plasma Pharmacokinetics of Ethanol Vulnerable Formulations

Hans Lennernäs*

Department of Pharmacy, Uppsala University, Se-751 23 Uppsala, Sweden

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Abstract: Generally, gastric emptying of a drug to the small intestine is controlled by gastric motor activity and is the main factor affecting the onset of absorption. Accordingly, the emptying rate from the stomach is mainly affected by the digestive state, the properties of the pharmaceutical formulation and the effect of drugs, posture and circadian rhythm. Variability in the gastric emptying of drugs is reflected in variability in the absorption rate and the shape of the plasma pharmacokinetic profile. When ethanol interacts with an oral controlled release product, such that the mechanism controlling drug release is impaired, the delivery of the dissolved dose into the small intestine and the consequent absorption may result in dangerously high plasma concentrations. For example, the maximal plasma concentration of hydromorphone has individually been shown to be increased as much as 16 times through *in vivo* testing as a result of this specific pharmacokinetic ethanol−drug formulation interaction. Thus, a pharmacokinetic ethanol−drug interaction is a very serious safety concern when substantially the entire dose from a controlled release product is rapidly emptied into the small intestine (dose dumping), having been largely dissolved in a strong alcoholic beverage in the stomach during a sufficient lag-time in gastric emptying. Based on the literature, a two hour time frame for screening the *in vitro* dissolution profile of a controlled release product in ethanol concentrations of up to 40% is strongly supported and may be considered as the absolute minimum standard. It is also evident that the dilution, absorption and metabolism of ethanol in the stomach are processes with a minor effect on the local ethanol concentration and that ethanol exposure will be highly dependent on the volume and ethanol concentration of the fluid ingested, together with the rate of intake and gastric emptying. When and in which patients a clinically significant dose dumping will happen is almost impossible to predict and will depend on drinking behavior and the highly variable gastrointestinal factors of importance for dissolution, transit and absorption. Therefore, controlled release products which show a vulnerability to ethanol during two hours *in vitro* should be required to demonstrate clinical safety by going through *in vivo* testing with an alcoholic beverage of up to 40% ethanol and of a sufficient volume (probably 120 mL or more), consumed in a relatively short period of time. Alternatively, such preparations should be reformulated in accordance with quality-by-design principles.

Keywords: Ethanol; controlled release; drug absorption; dose dumping; ethanol−drug interaction; opioids

Introduction

It is well-known that ethanol enhances the pharmacodynamic effects of opioids on the central nervous system (CNS). Recently, it has also been recognized that ingestion of ethanol will affect the plasma pharmacokinetics of some oral controlled release formulations such that the release rate from the dosage form is significantly increased, leading to an increase in the *in vivo* absorption rate and a complete change of the shape of the plasma concentration−time profile.[1] In these cases, the intended extended release plasma profile is replaced with a plasma profile that is usually

* Mailing address: Uppsala University, Dept. of Pharmacy, Husargtan 3, Box 580, Se-751 23 Uppsala, Sweden. Tel: +46 (0) 18 471 43 17. Fax: +46 (0) 18 471 42 23. E-mail: Hans.Lennernas@farmaci.uu.se.

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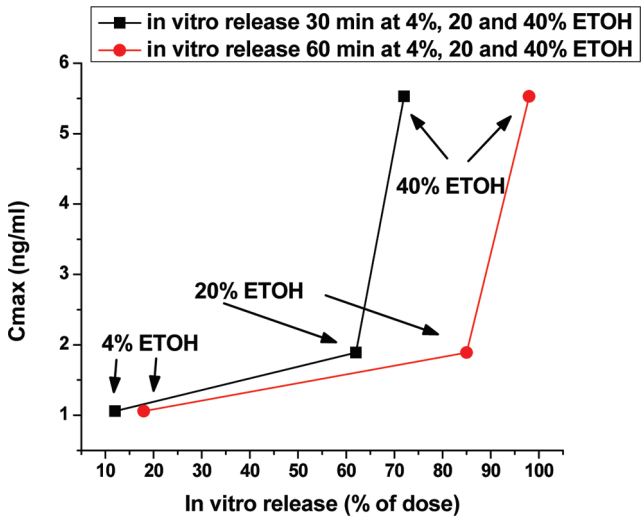

Figure 1. The relation between *in vitro* release and *in vivo* plasma exposure for hydromorphone at different ethanol doses. Hydromorphone in Palladone XL was given orally without ethanol and with ethanol at different oral doses (240 mL of 4% or 20% or 40% alcoholic beverage). The increased maximal exposure (Cmax) correlated to *in vitro* release data at both 30 and 60 min time points [data from Walden et al. (2007)[1]].

observed after oral administration of an immediate release dosage form or a solution. As the controlled release formulation in most cases contains a higher amount of active drug relative to an immediate release formulation, this sudden increased dissolution and absorption rate (dose dumping) may pose a serious safety issue because of the rapidly increased systemic exposure.

In one pharmacokinetic study, an oral once-daily controlled release product with hydromorphone (OAD hydromorphone formulation: Palladone XL) was administered orally as a single dose of 12 mg with 240 mL of ethanol at varying concentrations of 4%, 20% and 40% immediately before and/or together with the ingestion of the product (Figure 1).[1] The mean maximal plasma concentration (Cmax) ratio of hydromorphone was 1.1-, 1.9- and 5.5-fold at the respective ethanol concentrations of 4%, 20% and 40% compared with ingestion with water. However, it is worth emphasizing that one subject in this study experienced a 16-fold increase in Cmax after ingesting the OAD hydromorphone formulation with 40% alcohol. This *in vivo* study, which was the first to demonstrate a significant pharmacokinetic interaction with a controlled release dosage form and concomitant alcohol intake, illustrates that the dose dumping interaction is very individual, is extensive in some subjects and can be classified as a severe adverse effect.[1] This safety concern has prompted the conclusion that, in accordance with quality-by-design (QbD) principles, the most appropriate approach is to develop controlled release dosage forms which have robust release mechanisms in the presence of ethanol [Walden et al. (2007);[1] Henderson et al. (2007);[71] Roth et al. (2008);[69] 5 FDA Guidelines at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances]. Not surprisingly, the interaction described above resulted in the withdrawal of the OAD hydromorphone formulation from the US market[1] and the decision not to introduce the particular formulation in other territories.

The FDA has suggested in a number of recent drug specific guidelines to test the effect of different concentrations of ethanol [5, 20 and 40%; (vol/vol)] on *in vitro* dissolution (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances). These guidelines have been released for tramadol, oxymorphone, morphine sulfate, bupropion and the nonopiate metoprolol succinate. *In vitro* dissolution testing is a key tool to investigate whether the kinetics of a drug are affected by ethanol. The current bioequivalence guidelines and the biopharmaceutical classification system (BCS) provide a platform for a regulatory and safety assessment of the *in vitro* dissolution of controlled release dosage forms as a marker for consistency in clinical safety and efficacy.[2−4]

QbD has recently been introduced in pharmaceutical product development in a regulatory context, and the process of implementing such principles in the drug approval process is presently ongoing. Investigating ethanol vulnerability for controlled release dosage forms is a logical point of consideration in the context of QbD.[3] In accordance with regulatory guidelines, dissolution tests are used as a tool to identify formulation factors that affect—sometimes significantly—the bioavailability of the drug.[5]

The aim of this report is to analyze and discuss the current knowledge of how and when ethanol has a significant effect on the gastrointestinal absorption process of drugs in oral controlled release dosage forms, resulting in dose dumping. In addition, a suggested *in vitro* approach to examine and predict this interaction will be discussed. More specifically, the validity of applying the 2 h *in vitro* release test as a screening for the relevance of conducting clinical ethanol−drug interaction studies will be scrutinized.

Definition of Gastrointestinal Absorption and the Factors of Importance

Most drugs administered orally have a pharmacological effect(s) related to the rate and extent of absorption and

(1) Walden, M.; Nicholls, F. A.; Smith, K. J.; Tucker, G. T. The effect of ethanol on the release of opioids from oral prolonged-release preparations. *Drug Dev. Ind. Pharm.* **2007**, *33*, 1101–11.

(2) Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* **1995**, *12*, 413–20.

(3) Dickinson, P. A.; Lee, W. W.; Stott, P. W.; Townsend, A. I.; Smart, J. P.; Ghahramani, P.; Hammett, T.; Billett, L.; Behn, S.; Gibb, R. C.; Abrahamsson, B. Clinical relevance of dissolution testing in quality by design. *AAPS J.* **2008**, *10*, 380–90.

(4) Yu, L. X. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm. Res.* **2008**, *25*, 781–91.

(5) Lennernas, H.; Abrahamsson, B. The use of biopharmaceutic classification of drugs in drug discovery and development: current status and future extension. *J. Pharm. Pharmacol.* **2005**, *57*, 273–85.

bioavailability of the active drug form(s). Bioavailability (F) is the most useful pharmacokinetic variable for characterizing the fraction of an oral dose that reaches the systemic circulation in an unchanged (active) form. In a regulatory context, bioavailability is also understood to be the rate and extent to which an active substance delivered from a pharmaceutical dosage form becomes available in the general circulation. Bioavailability is mainly dependent on three general but rather complex serial processes; the fraction of dose absorbed (fa), the first-pass extraction of the drug in the gut wall (E_G) and the first-pass extraction of the drug in the liver (E_H) (eq 1).[2,6−11]

$$F = \text{fa} \cdot (1 - E_G) \cdot (1 - E_H) \quad (1)$$

Accordingly, the rate (mass/time) and extent of drug absorption (fa = mass/dose) from the intestinal lumen *in vivo* are influenced by dose/dissolution ratio, chemical degradation or metabolism in the lumen, luminal complex binding, intestinal transit and effective intestinal permeability (P_{eff}) across the intestinal mucosa. The fraction of the dose absorbed (fa = $M(t)$/dose), i.e. the fraction of drug that is lost from the intestinal lumen, assuming no luminal reactions, at any time t is

$$\text{fa} = \frac{M(t)}{\text{dose}} = \frac{1}{\text{dose}} \int_0^t \int_A P_{\text{eff}} \cdot C_{\text{lumen}} \, dA' \, dt' \quad (2)$$

where A is the available intestinal surface area, P_{eff} is the average value of the effective intestinal permeability along the intestinal region where absorption occurs, and C_{lumen} is the free reference concentration of the drug in the intestinal lumen available for absorption.[2] From eq 2 it is clear that the P_{eff} and the dissolved and free drug concentrations are the key variables controlling the overall rate and extent of absorption and the equation is thus applicable regardless of the transport mechanism.[2,12−14] Accordingly, in this particular case where ethanol induces a sudden increase in the dissolution rate of the controlled release dosage form, the resulting higher luminal drug concentration (C_{lumen}) will lead to a proportional increase in intestinal absorption rate and bioavailability (dose dumping) (see eq 2).

Gastrointestinal Factors of Importance for the Ethanol−Drug Absorption Interaction

Gastric emptying has a crucial role for the onset of drug absorption. Various factors can prolong gastric emptying, which means, in the case of an ethanol vulnerable formulation, that the risk of dose dumping is increased when high concentrations of ethanol are present in the stomach. The possibility of significant exposure of the drug to high concentrations of ethanol will also depend on the local concentration−time profile of ethanol in the stomach, as determined by oral intake, gastric dilution, metabolism, absorption and emptying. This ethanol profile, together with the properties of the dosage form (such as surface area, solubility of the drug in ethanol and acid gastric fluids and solubility of the pharmaceutical excipients), will determine the risk of a dose dumping. This safety issue has to be considered for all types of controlled release dosage forms, since ingestion of various alcoholic beverages is a very common habit in most cultures.

This section will focus on the gastrointestinal factors of importance for the ethanol−drug absorption interaction.

Site of Drug Absorption. Today it is well-established that drugs, ethanol and nutrients are absorbed mainly in the small intestine after oral intake. Formerly, there was a conception that low molecular weight and highly permeable neutral compounds as well as weakly acidic lipid soluble drugs were rapidly absorbed from the stomach. However, this is certainly not the case: acetylsalicylic acid, warfarin, paracetamol and caffeine are examples of drugs that are absorbed much more rapidly from the small intestine than from the stomach in humans.[15−18] Similar findings have been described with phenobarbitone, pentobarbitone, promethazine and ethanol in rats.[19,20] Magnussen also investigated the direct effect of ethanol on the absorption of drugs in solution in rats and

(6) Lindahl, A.; Sandstrom, R.; Ungell, A. L.; Abrahamsson, B.; Knutson, T. W.; Knutson, L.; Lennernas, H. Jejunal permeability and hepatic extraction of fluvastatin in humans. *Clin. Pharmacol. Ther.* **1996**, *60*, 493–503.

(7) Wu, C. Y.; Benet, L. Z. Predicting drug disposition via application of BCS: transport/absorption/ elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharm. Res.* **2005**, *22*, 11–23.

(8) Wu, C. Y.; Benet, L. Z.; Hebert, M. F.; Gupta, S. K.; Rowland, M.; Gomez, D. Y.; Wacher, V. J. Differentiation of absorption and first-pass gut and hepatic metabolism in humans: studies with cyclosporine. *Clin. Pharmacol. Ther.* **1995**, *58*, 492–7.

(9) Cummins, C. L.; Salphati, L.; Reid, M. J.; Benet, L. Z. In vivo modulation of intestinal CYP3A metabolism by P-glycoprotein: studies using the rat single-pass intestinal perfusion model. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 306–14.

(10) Sinko, P. J.; Leesman, G. D.; Amidon, G. L. Predicting fraction dose absorbed in humans using a macroscopic mass balance approach. *Pharm. Res.* **1991**, *8*, 979–88.

(11) Dressman, J. B.; Amidon, G. L.; Fleisher, D. Absorption potential: estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* **1985**, *74*, 588–9.

(12) Lennernas, H. Human intestinal permeability. *J. Pharm. Sci.* **1998**, *87*, 403–10.

(13) Lennernas, H.; Crison, J. R.; Amidon, G. L. Permeability and clearance views of drug absorption: a commentary. *J. Pharmacokinet. Biopharm.* **1995**, *23*, 333–43.

(14) Bourdet, D. L.; Pollack, G. M.; Thakker, D. R. Intestinal absorptive transport of the hydrophilic cation ranitidine: a kinetic modeling approach to elucidate the role of uptake and efflux transporters and paracellular vs. transcellular transport in Caco-2 cells. *Pharm. Res.* **2006**, *23*, 1178–87.

(15) Siurala, M.; Mustala, O.; Jussila, J. Absorption of acetylsalicylic acid b a normal and an atrophic gastic mucosa. *Scand. J. Gastroenterol.* **1969**, *4*, 269–73.

(16) Kekki, M.; Pyorala, K.; Mustala, O.; Salmi, H.; Jussila, J.; Siurala, M. Multicompartment analysis of the absorption kinetics of warfarin from the stomach and small intestine. *Int. Z. Klin. Pharmakol. Ther. Toxikol.* **1971**, *5*, 209–11.

showed that it was dependent on the physicochemical properties and the localization in the gastrointestinal tract.

The onset of intestinal absorption of drugs with sufficiently high intestinal permeability will depend almost entirely on the rate of gastric emptying. The clinical importance of this effect is illustrated by the therapeutic success of L-DOPA in patients with a duodenal infusion by avoiding the highly variable and sometimes delayed gastric emptying.[21] A further evidence for the fact that the small intestine is the main absorbing region of xenobiotics (such as drugs and ethanol) is the well-established delaying effect of GLP-1 analogues (glucagon-like peptide-1 that shares some of the glucoregulatory actions of GLP-1) on gastric emptying, which means that there is a lag period before absorption is initiated. It has been reported that exenatide (a GLP-1 analogue) delays the absorption rate for digoxin, warfarin, paracetamol, lisinopril and lovastatin.[22−24]

In Figure 2 there is a correlation between plasma pharmacokinetics (Cmax, tmax) of paracetamol, a drug with BCS class I behavior (high solubility; high permeability) and measured gastric emptying (^{113}In DTPA, 300 mCi, as a nonabsorbable isotopic marker) that strongly supports that this drug and other xenobiotics are mainly absorbed in the intestine.[25] This early study demonstrated the crucial role of gastric emptying for the onset of drug absorption, which was further confirmed just recently in ref 18.

Gastric Emptying Rate and Its Effect on Drug Absorption. Higaki et al. (2008)[18] reported that gastric emptying is a very complex process in the fasted state and that there is a significant lag-time (i.e. a period of no or minimal gastric emptying) which directly correlates to the fasted motility pattern (interdigestive myoelectric migrating complex, IMMC). The IMMC has three distinct phases: the first phase is quiescent, the second phase has an erratic contractility and the third phase is characterized by intense activity, which is associated with a transit of chyme in the distal direction in the gastrointestinal tract. In most subjects, the onset of absorption in the fasted state correlated to the initiation of motility phase 2, which resulted in some healthy subjects having a relatively long lag-time in gastric emptying with the onset of drug absorption occuring after 120−180 min.[18,26] Figure 3 demonstrates the large interindividual variability in intestinal motility, gastric emptying and onset of drug absorption from the intestine in healthy young

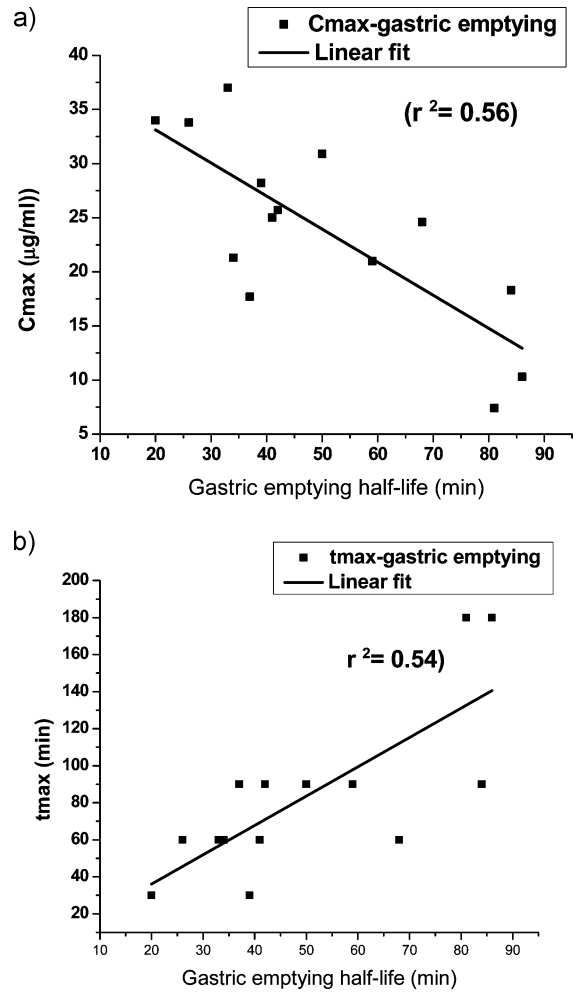

Figure 2. (a) The correlation between gastric emptying measured with a radioisotope method and the plasma pharmacokinetics of paracetamol (Cmax) in young healthy volunteers [data from Heading et al. (1973)[25]]. (b) The correlation between gastric emptying measured with a radioisotope method and the plasma pharmacokinetics of paracetamol (tmax) in young healthy volunteers [data from Heading et al. (1973)[25]].

(17) Naslund, E.; Bogefors, J.; Gryback, P.; Jacobsson, H.; Hellstrom, P. M. Gastric emptying: comparison of scintigraphic, polyethylene glycol dilution, and paracetamol tracer assessment techniques. *Scand. J. Gastroenterol.* **2000**, *35*, 375–9.

(18) Higaki, K.; Choe, S. Y.; Lobenberg, R.; Welage, L. S.; Amidon, G. L. Mechanistic understanding of time-dependent oral absorption based on gastric motor activity in humans. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 313–25.

(19) Magnussen, M. P. The effect of ethanol on the gastrointestinal absorption of drugs in the rat. *Acta Pharmacol. Toxicol. (Copenhagen)* **1968**, *26*, 130–44.

(20) Kojima, S.; Smith, R. B.; Doluisio, J. T. Drug absorption. V. Influence of food on oral absorption of phenobarbital in rats. *J. Pharm. Sci.* **1971**, *60*, 1639–41.

(21) Nyholm, D.; Askmark, H.; Gomes-Trolin, C.; Knutson, T.; Lennernas, H.; Nystrom, C.; Aquilonius, S. M. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clin. Neuropharmacol.* **2003**, *26*, 156–63.

(22) Soon, D.; Kothare, P. A.; Linnebjerg, H.; Park, S.; Yuen, E.; Mace, K. F.; Wise, S. D. Effect of exenatide on the pharmacokinetics and pharmacodynamics of warfarin in healthy Asian men. *J. Clin. Pharmacol.* **2006**, *46*, 1179–87.

(23) Kothare, P. A.; Linnebjerg, H.; Skrivanek, Z.; Reddy, S.; Mace, K.; Pena, A.; Han, J.; Fineman, M.; Mitchell, M. Exenatide effects on statin pharmacokinetics and lipid response. *Int. J. Clin. Pharmacol. Ther.* **2007**, *45*, 114–20.

(24) Kothare, P. A.; Soon, D. K.; Linnebjerg, H.; Park, S.; Chan, C.; Yeo, A.; Lim, M.; Mace, K. F.; Wise, S. D. Effect of exenatide on the steady-state pharmacokinetics of digoxin. *J. Clin. Pharmacol.* **2005**, *45*, 1032–7.

(25) Heading, R. C.; Nimmo, J.; Prescott, L. F.; Tothill, P. The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.* **1973**, *47*, 415–21.

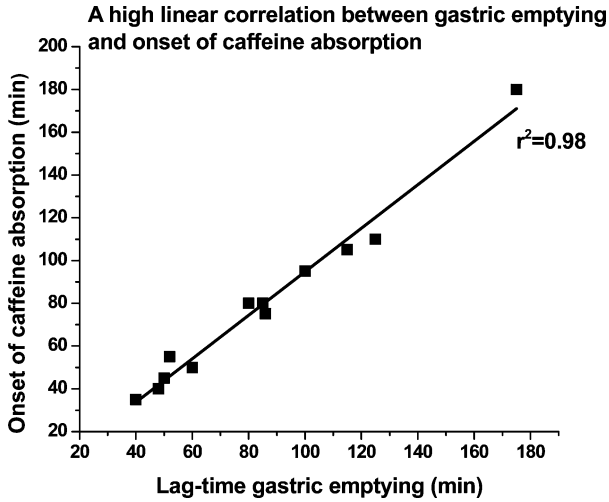

Figure 3. A high correlation between gastric emptying measured with a radioisotope method and the onset of caffeine absorption in young healthy volunteers [Higaki et al. (2008)[18]].

subjects after a coadministration of spherical enteric-coated caffeine pellets (0.7 mm in diameter) and a 200 mL viscous meal containing 100 kcal.[18] However, it is clear from looking at the overall picture that there is a strong correlation between gastric emptying time profiles (based on gastric motor activity-based model) and onset of absorption (calculated from plasma concentrations of caffeine).[18]

The data reported in Higaki et al. (2008)[18] are crucial as they show that gastric retention time may be longer than 2 h even in a light fed state in healthy subjects, which directly validates the physiological relevance of applying a 2 h *in vitro* drug dissolution experiment as a prognostic test for determining any ethanol sensitivity. The energy load in the liquid meal used by Higaki et al.[18] in 2008 was comparable to the energy load in many alcoholic beverages.[18,27] Higaki et al.[18] in 2008 also clearly showed that while there may be significant lag-times in gastric emptying, the process can be quite rapid once started. Therefore, it is entirely physiologically possible that an alcoholic beverage, even without any additional caloric content from fat or sugar, might have a gastric residence sufficiently long to dissolve the major part of a controlled release dose, which is then suddenly and swiftly emptied into the intestine. Such a process should be considered as dose dumping even if it occurred 90−150 min post dosing.[27] The gastric emptying *per se* may be quite rapid once it is started, but the overall measured rate is slow because of this lag period with no or minimal gastric emptying.[18] In the drug usage situation there will be additional factors that may prolong gastric residence time to at least 2 h and even longer, such as treatment with other drugs, alcohol consumption, gastric dysmotility and paresis, circadian rhythm, posture, different types of meals, disease and age[25,28−34] [Langguth et al. (1994);[75] Nyholm et al. (2003);[21] Higaki et al. (2008)[18]]. These factors have also to be considered in the analysis of this specific ethanol−drug interaction.

It is obvious that other drugs affect the onset and rate of drug absorption by influencing the rate of gastric emptying. For instance, it has been demonstrated that two opioids, pethidine and diamorphine, prolong the gastric emptying time.[32,33] Pethidine (a single im dose of 150 mg) prolongs the mean time for 50% gastric emptying of the ingested solution (400 mL of orange juice containing paracetamol 20 mg/kg together with ^{113}In DTPA 300 mCi as a nonabsorbable isotopic marker for the emptying measurement) to 89.5 ± 11.9 min (Figure 4). The opioid diamorphine (a single im dose of 10 mg) largely inhibited gastric emptying for more than 90 min in three of four subjects and none achieved 50% emptying of the stomach within two hours (Figure 4).

In the fed state, the pylorus is not completely closed during digestion and pharmaceutical dosage forms can be emptied out of the stomach during this digestive state. Gastric muscle contractions grind and mix solid/liquid meal within the stomach, and move it into the bowels at a controlled rate. In a study reported by Tougas et al. in 2000, the gastric emptying scintigraphy (GES) was used to measure the gastric emptying of a ^{99}Tc-labeled low fat meal (caloric value of 255 kcal; nutritional composition: 72% carbohydrate, 24% protein, 2% fat and 2% fiber) in 123 healthy volunteers (60 women and 63 men; mean age 41 yr, range 19−73 yr) with no history of GI illness or surgery and without any other ongoing medical condition.[35,36] The gastric emptying data (median T_{50}) for this nutritional liquid was 83 min (first and

(26) Oberle, R. L.; Chen, T. S.; Lloyd, C.; Barnett, J. L.; Owyang, C.; Meyer, J.; Amidon, G. L. The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterology* **1990**, *99*, 1275–82.

(27) Franke, A.; Teyssen, S.; Harder, H.; Singer, M. V. Effect of ethanol and some alcoholic beverages on gastric emptying in humans. *Scand. J. Gastroenterol.* **2004**, *39*, 638–44.

(28) Weathermon, R.; Crabb, D. W. Alcohol and medication interactions. *Alcohol Res. Health* **1999**, *23*, 40–54.

(29) Goo, R. H.; Moore, J. G.; Greenberg, E.; Alazraki, N. P. Circadian variation in gastric emptying of meals in humans. *Gastroenterology* **1987**, *93*, 515–8.

(30) Renwick, A. G.; Ahsan, C. H.; Challenor, V. F.; Daniels, R.; Macklin, B. S.; Waller, D. G.; George, C. F. The influence of posture on the pharmacokinetics of orally administered nifedipine. *Br. J. Clin. Pharmacol.* **1992**, *34*, 332–6.

(31) Moore, J. G.; Datz, F. L.; Christian, P. E.; Greenberg, E.; Alazraki, N. Effect of body posture on radionuclide measurements of gastric emptying. *Dig. Dis. Sci.* **1988**, *33*, 1592–5.

(32) Nimmo, W. S.; Heading, R. C.; Wilson, J.; Tothill, P.; Prescott, L. F. Inhibition of gastric emptying and drug absorption by narcotic analgesics. *Br. J. Clin. Pharmacol.* **1975**, *2*, 509–13.

(33) Nimmo, W. S.; Wilson, J.; Prescott, L. F. Narcotic analgesics and delayed gastric emptying during labour. *Lancet* **1975**, *1*, 890–3.

(34) Nimmo, W. S. Drugs, diseases and altered gastric emptying. *Clin. Pharmacokinet.* **1976**, *1*, 189–203.

(35) Tougas, G.; Eaker, E. Y.; Abell, T. L.; Abrahamsson, H.; Boivin, M.; Chen, J.; Hocking, M. P.; Quigley, E. M.; Koch, K. L.; Tokayer, A. Z.; Stanghellini, V.; Chen, Y.; Huizinga, J. D.; Ryden, J.; Bourgeois, I.; McCallum, R. W. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am. J. Gastroenterol.* **2000**, *95*, 1456–62.

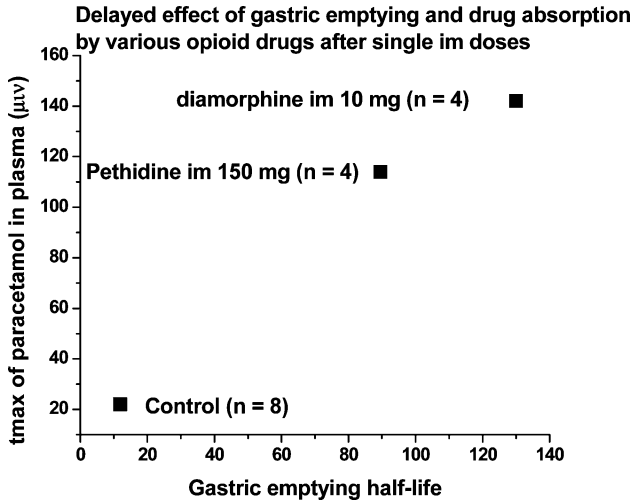

Figure 4. The correlation between gastric emptying measured with a radioisotope method and the plasma pharmacokinetics of paracetamol (tmax) in young healthy volunteers when they were treated with a single intramuscular (im) dose of either pethidine or diamorphine [data from Nimmo et al. (1975)[32]].

third quartiles were 64 and 103 min, respectively) and the lag phase 21 min (first and third quartiles were 12 and 36 min, respectively).

It has also been reported that ethanol at low concentrations (4% and 10%) prolongs the gastric emptying times of solid meals, but the effect of ethanol was independent of the caloric content of the meal. Interestingly, Franke et al. in 2005 reported that the inhibitory effect was mainly related to an effect of prolongation of the gastric emptying phase, which did not affect the lag phase.[37] In general, the inhibitory effect is more dependent on the caloric content of the beverage than the ethanol itself. It is also less of risk that ethanol will affect the dissolution rate in the full fed state since the stomach is then extensively diluted with the ingested meal.

Local Concentration−Time Profile of Ethanol in the Stomach

Dilution of Ethanol. In a study reported by Schiller et al. (2005), water-sensitive magnetic resonance imaging was performed on 12 healthy subjects during fasting and also 1 h after a meal to assess the fluid volume at different regions of the human gastrointestinal system.[38] In the fasted state, residual fluid volumes between 13 and 72 mL were found in the stomach, with a median value of 47 mL. Overall, these volumes indicate that the residual fluid in the stomach does not significantly contribute to the dilution of any alcoholic beverage in the fasted state. However, the dilution of an alcoholic beverage will be affected by coingested volumes during a meal. In the same report by Schiller et al.,[38] the fed state was investigated by serving a meal that consisted of total 13.7% fat, 23.1% protein and 63.2% carbohydrates (803 kcal, 3381 kJ). The total volume of the meal was 900 mL as determined after homogenization of all meal components. In the fed state, fluid volumes of between 534 and 859 mL were found in the stomach, with a median value of 701 mL.[38] In the fasted state, the residual fluid volume tends to be about 45 mL in the stomach (although this figure is highly variable), which means that there will be a rather minor dilution of a sufficiently large ingested volume of strong alcohol (for instance 120 mL of 40% whisky/vodka) in the stomach in many subjects. It is clear that gastric dilution is minimal in the fasted state and highly dependent on the volume swallowed in the fed state.

The secretion response of the stomach following oral intake of ethanol has been reported in studies based on intragastric infusion of various ethanol containing beverages.[39−41] The action of intragastric administered ethanol in various concentrations (1.4%−40%) and of beer, white wine, cognac, and whisky on gastric acid secretion and release of gastrin has been investigated in healthy humans. Ethanol concentrations of 1.4% and 4%, but not higher, had a moderate effect on gastric acid secretion to 23% and 22%, respectively (compared to a physiological based stimulant, pentagastrin). The gastric acid responses of incremental maximal acid output to beer and white wine were 96% and 61% in relation to the control acid secretion, respectively, but neither cognac nor whisky had any stimulatory effect.[40] In another study, intragastric infusion was performed to simulate normal ingestion of alcoholic beverages. When compared to saline (control), none of the pure ethanol solutions increased serum gastrin concentration or gastric acid secretion significantly. In contrast, red and white wines (12% ethanol vol/vol) were potent stimulants of gastrin release and acid secretion when compared either to saline or pure 12% ethanol.[41]

(36) Tougas, G.; Chen, Y.; Coates, G.; Paterson, W.; Dallaire, C.; Pare, P.; Boivin, M.; Watier, A.; Daniels, S.; Diamant, N. Standardization of a simplified scintigraphic methodology for the assessment of gastric emptying in a multicenter setting. *Am. J. Gastroenterol.* **2000**, *95*, 78–86.

(37) Franke, A.; Nakchbandi, I. A.; Schneider, A.; Harder, H.; Singer, M. V. The effect of ethanol and alcoholic beverages on gastric emptying of solid meals in humans. *Alcohol Alcohol.* **2005**, *40*, 187–93.

(38) Schiller, C.; Frohlich, C. P.; Giessmann, T.; Siegmund, W.; Monnikes, H.; Hosten, N.; Weitschies, W. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment. Pharmacol. Ther.* **2005**, *22*, 971–9.

(39) Chari, S.; Teyssen, S.; Singer, M. V. Alcohol and gastric acid secretion in humans. *Gut* **1993**, *34*, 843–7.

(40) Singer, M. V.; Leffmann, C.; Eysselein, V. E.; Calden, H.; Goebell, H. Action of ethanol and some alcoholic beverages on gastric acid secretion and release of gastrin in humans. *Gastroenterology* **1987**, *93*, 1247–54.

(41) Peterson, W. L.; Barnett, C.; Walsh, J. H. Effect of intragastric infusions of ethanol and wine on serum gastrin concentration and gastric acid secretion. *Gastroenterology* **1986**, *91*, 1390–5.

These studies clearly demonstrate that there was no effect (rather an inhibitory effect) of pure ethanol on gastric acid secretion in the concentration range of 5%−40%. However, beer, red and white wine, but not whisky and cognac, were potent stimulants of gastric acid secretion.[39−41] The non-alcoholic constituents of beer and wine are most likely responsible for the stimulatory actions of both beverages on gastric acid secretion and release of gastrin. These reports clearly show that oral ingestion of an ethanol sensitive controlled release product before, at the same time or after intake of strong alcoholic beverages (such as gin, vodka, schnapps, whisky and cognac) in the fasted state will lead to an extremely limited dilution as a consequence of the negligible gastric secretion and the rather low volume present in the stomach.[38] This certainly increases the risk that ethanol present in the stomach can destroy the controlled release mechanism(s) of an ethanol sensitive controlled release product, since sufficiently high ethanol gastric concentrations can be obtained. It also further validates the *in vitro* dissolution test suggested by the FDA for ethanol concentrations between 0 and 40% to take place during two hours (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances).

Absorption of Ethanol. It is well-established that there exists a close relationship between gastric emptying and ethanol absorption when alcohol is consumed in the fasted state. The rate of alcohol absorption is increased by metoclopramide and is slowed by drugs that delay gastric emptying such as opioids and anticholinergic agents.[42−47] Blood alcohol concentrations are depressed by intraintestinal fat infusions, fat and alcohol being two factors that normally slow gastric emptying.[48] Further evidence that gastric emptying is the major physiological factor determining the residence and mixing time for ethanol and the dosage form is a report on a modified physiological based pharmacokinetic model for ethanol. In particular, the *in silico* simulation showed that an inclusion of the retardation of gastric emptying improved the ability of the theoretical model to describe the *in vivo* performance during the absorption phase and up to the peak venous blood level of ethanol.[49]

It has recently been reported that about 10−20% of orally ingested ethanol is absorbed from the stomach and 80−90% is absorbed from the small intestine by passive diffusion.[50−52] It is also considered that all ingested ethanol is absorbed and only a minor fraction, probably significantly less than 5%, is metabolized in the stomach.[53] Ethanol is a small neutral molecule with high passive membrane permeability. However, the rather small surface area of the stomach epithelium, especially in comparison with the small intestine, and the fact of the stomach having minimal absorption capacity, is the major explanation for the difference. Instead, the stomach efficiently grinds and mixes its content before emptying it into the small intestine.

Metabolism of Ethanol. Elimination of ethanol is principally by metabolism in the liver with small amounts excreted in the breath (0.7%), urine (0.3%), and sweat (0.1%).[52] Metabolism of ethanol in the gastric mucosa is probably very limited, <5%.[53,54] Accordingly metabolism in the liver is the major organ for elimination, and it has been accounted for 92−95% of the total elimination.[52,53] Metabolism occurs by the cytosolic alcohol dehydrogenases (ADH) and aldehyde dehydrogenases (ALDH) and to a minor extent by the microsomal cytochrome P450 2E1 (CYP2E1).[55−62]

(42) Gibbons, D. O.; Lant, A. F. Effects of intravenous and oral propantheline and metoclopramide on ethanol absorption. *Clin. Pharmacol. Ther.* **1975**, *17*, 578–84.
(43) Horowitz, M.; Maddox, A.; Bochner, M.; Wishart, J.; Bratasiuk, R.; Collins, P.; Shearman, D. Relationships between gastric emptying of solid and caloric liquid meals and alcohol absorption. *Am. J. Physiol.* **1989**, *257*, G291–8.
(44) Linseman, M. A.; Le, A. D. Effects of opioids on the absorption of alcohol. *Pharmacol., Biochem. Behav.* **1997**, *58*, 79–84.
(45) Crighton, I. M.; Martin, P. H.; Hobbs, G. J.; Cobby, T. F.; Fletcher, A. J.; Stewart, P. D. A comparison of the effects of intravenous tramadol, codeine, and morphine on gastric emptying in human volunteers. *Anesth. Analg.* **1998**, *87*, 445–9.
(46) Horowitz, M.; Su, Y. C.; Rayner, C. K.; Jones, K. L. Gastroparesis: prevalence, clinical significance and treatment. *Can. J. Gastroenterol.* **2001**, *15*, 805–13.
(47) Kechagias, S.; Jonsson, K. A.; Jones, A. W. Impact of gastric emptying on the pharmacokinetics of ethanol as influenced by cisapride. *Br. J. Clin. Pharmacol.* **1999**, *48*, 728–32.
(48) McFarlane, A.; Pooley, L.; Welch, I. M.; Rumsey, R. D.; Read, N. W. How does dietary lipid lower blood alcohol concentrations. *Gut* **1986**, *27*, 15–8.
(49) Loizou, G. D.; Spendiff, M. A human PBPK model for ethanol describing inhibition of gastric motility. *J. Mol. Histol.* **2004**, *35*, 687–96.
(50) Lavo, B.; Colombel, J. F.; Knutsson, L.; Hallgren, R. Acute exposure of small intestine to ethanol induces mucosal leakage and prostaglandin E2 synthesis. *Gastroenterology* **1992**, *102*, 468–73.
(51) Levitt, D. G. PKQuest: measurement of intestinal absorption and first pass metabolism - application to human ethanol pharmacokinetics. *BMC Clin. Pharmacol.* **2002**, *2*, 4.
(52) Norberg, A.; Jones, A. W.; Hahn, R. G.; Gabrielsson, J. L. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. *Clin. Pharmacokinet.* **2003**, *42*, 1–31.
(53) Levitt, M. D.; Li, R.; DeMaster, E. G.; Elson, M.; Furne, J.; Levitt, D. G. Use of measurements of ethanol absorption from stomach and intestine to assess human ethanol metabolism. *Am. J. Physiol.* **1997**, *273*, G951–7.
(54) Seitz, H. K.; Poschl, G. The role of gastrointestinal factors in alcohol metabolism. *Alcohol Alcohol.* **1997**, *32*, 543–9.
(55) Lieber, C. S. New pathway of ethanol metabolism in the liver. *Gastroenterology* **1970**, *59*, 930–7.
(56) Lieber, C. S.; Rubin, E.; DeCarli, L. M. Hepatic microsomal ethanol oxidizing system (MEOS): differentiation from alcohol dehydrogenase and NADPH oxidase. *Biochem. Biophys. Res. Commun.* **1970**, *40*, 858–65.
(57) Coon, M. J.; Koop, D. R.; Reeve, L. E.; Crump, B. L. Alcohol metabolism and toxicity: role of cytochrome P-450. *Fundam. Appl. Toxicol.* **1984**, *4*, 134–43.
(58) Bosron, W. F.; Li, T. K. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. *Hepatology* **1986**, *6*, 502–10.

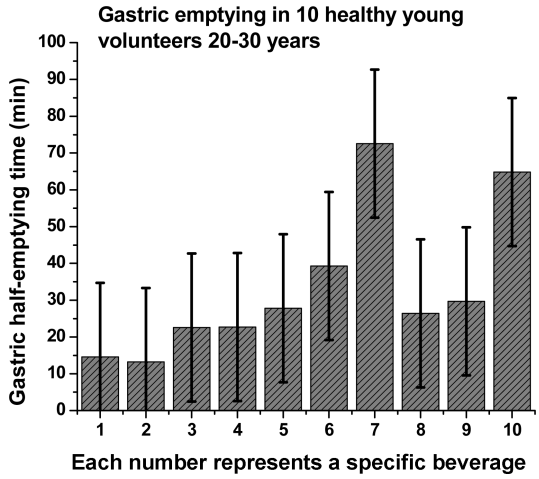

Figure 5. The correlation between gastric emptying measured with an ultrasonograph method following dosing of alcoholic containing beverages and other fluids in young healthy volunteers [data from Franke et al. (2004)[27]]. 1 = water 500 mL; 2 = water 250 mL; 3 = ethanol 4%; 4 = ethanol 10%; 5 = ethanol 40%; 6 = beer 500 mL; 7 = red wine 500 mL; 8 = whisky 125 mL; 9 = glucose solution 5.5% 500 mL; 10 = glucose solution 11.4% 500 mL.

Gastric Emptying Rate of Ethanol. Alcoholic beverages and pure ethanol have a delaying effect on gastric emptying of both liquids and solid meals regardless of their energy load when compared to water.[27,37] In a study by Franke et al. the effect of beer, red wine, whisky, pure ethanol, water and glucose containing solutions on gastric emptying in 10 healthy young subjects (20−30 years) was assessed by ultrasonography.[27] The effects various beverages have on half-emptying times are provided in Figure 5, and it is clear that fermented beverages and those with carbohydrates (beer and red wine) have a significantly prolonged gastric emptying rate as compared with other beverages containing ethanol.[27] Whisky and pure 40% alcohol have a mean half-emptying time in fasted healthy young subjects of about 30 min. Even though these data are obtained in healthy young subjects, they may be representative of the rank order between various beverages regarding gastric emptying in a more probable patient population. But they will certainly not reflect the expected absolute delay of gastric emptying from various alcoholic beverages in patients. It is important to recognize that further delays are expected when elderly people with various diseases are treated with drugs (such as opioids and anticholinergic agents) that significantly prolong gastric residence time as shown in Figure 4.

In the case of an elderly patient who is dosed at steady state with an opioid drug and who takes a large glass of whisky perhaps together with Coke (glucose), some peanuts/crisps (fats and carbohydrates) and then lies down (digestive and posture effects), several synergistic factors will work to significantly prolong the gastric residence time.[27,29,30,63] Altogether, these observations strongly support a benchmark of *in vitro* dissolution testing of 2 h, which will be realistic in various situations for patients as they may have gastric residence times up to even 2 h and longer.

Ethanol Vulnerability As a Formulation Dependent Problem

Controlled release formulations by definition contain large amounts of drug in most cases; thus the release mechanisms must be sufficiently robust to prevent any possibility of uncontrolled rapid release rate in the presence of ethanol (dose dumping). This is especially important for opioid drugs such as hydromorphone, tramadol, oxycodone and morphine because opioids can prolong gastric emptying which in turn increases the risk of a sufficiently long exposure to high concentrations of ethanol in the stomach.[32,33,42,64] Based on the discussion above, this means that the opioid formulation may be exposed to ethanol for quite a prolonged period of time. While opioid drugs can cause clinically severe side-effects (due to their pharmacodynamics), this specific pharmacokinetic interaction poses a more unpredictable—and potentially more dangerous—risk to patients. Accordingly, all prolonged release drugs should be tested *in vitro* for vulnerability to ethanol. In circumstances where the formulation is shown through *in vitro* testing to be vulnerable to ethanol, *in vivo* testing or reformulation in accordance with QbD principles should be a regulatory requirement. These quality principles should focus on developing pharmaceutical products that are robust and which are not affected by factors common to patients such as the ingestion of alcoholic beverages. In addition, when and in which patients a clinically significant dose dumping will occur is almost impossible to predict, but relevant factors include the different drinking behavior of patients and the high intra- and interindividual variability in gastrointestinal factors of importance for solubility/dissolution as well as gastrointestinal transit and absorption. It is also important to recognize that such an interaction is even more serious for patients with lung diseases as the high concentrations of the opioid will affect those CO_2-receptors controlling the respiration.

(59) Kitson, K. E. Ethanol and acetaldehyde metabolism: past, present, and future. *Alcohol.: Clin. Exp. Res.* **1996**, *20*, 82A–92A.
(60) Dilger, K.; Metzler, J.; Bode, J. C.; Klotz, U. CYP2E1 activity in patients with alcoholic liver disease. *J. Hepatol.* **1997**, *27*, 1009–14.
(61) Agarwal, D. P. Genetic polymorphisms of alcohol metabolizing enzymes. *Pathol. Biol. (Paris)* **2001**, *49*, 703–9.
(62) Okamoto, K.; Murawaki, Y.; Yuasa Kawasaki, H. Effect of ALDH2 and CYP2E1 gene polymorphisms on drinking behavior and alcoholic liver disease in Japanese male workers. *Alcohol.: Clin. Exp. Res.* **2001**, *25*, 19S–23S.
(63) Fraser, A. G.; Rosalki, S. B.; Gamble, G. D.; Pounder, R. E. Inter-individual and intra-individual variability of ethanol concentration-time profiles: comparison of ethanol ingestion before or after an evening meal. *Br. J. Clin. Pharmacol.* **1995**, *40*, 387–92.
(64) Nimmo, W. S.; Wilson, J.; Prescott, L. F. Proceedings: Narcotic analgesics and delayed gastric emptying in labour. *Anaesthesia* **1975**, *30*, 119.

As explained above, an oral OAD hydromorphone formulation was withdrawn from the US market because *in vivo* testing showed that simultaneous strong alcohol intake (40%) increased the plasma exposure in some individuals. These *in vivo* results were foreshadowed by the results of *in vitro* ethanol dissolution testing over a 2 h period which showed that the *in vitro* release of hydromorphone was affected by ethanol in the dissolution media.[1] This enhanced *in vitro* and *in vivo* drug release was explained by a breakdown of the controlled release function of this formulation (a consequence of its design) and the higher solubility of these pharmaceutical excipients in the presence of ethanol.

The *in vitro* drug release is ethanol concentration dependent, and, in the case of the OAD hydromorphone formulation, became especially sensitive at ethanol concentrations above 24% in the *in vitro* dissolution media. It is clear that 62%−72% and 85%−98% of the hydromorphone dose is released within 30 and 60 min for 20% and 40% of ethanol, respectively (Figure 1). As a comparison the *in vitro* release of hydromorphone was about 5% and 10% at 30 and 60 min in control experiments, respectively [Walden et al. (2007)[1]].

In the *in vivo* pharmacokinetic study with the OAD hydromorphone formulation, it was found that the mean maximum plasma (Cmax) of hydromorphone increased by 1.9 times (range 0.94−5.72) and 5.5 times (range 0.77−15.8) from a 12 mg dose together with 240 mL of 20% and 40% ethanol solutions, respectively.[1] These tmax values occurred in general about 1 h after dosing with high concentration of ethanol. Normally the first tmax for controlled release formulation of hydromorphone was reported to be around 3−4 h and the second tmax about 12−16 h following single-dose administration.[65] In any individual there is a relationship between plasma concentration and opioid effects; thus it can be concluded that the plasma concentration measurements are useful as surrogate markers.[66] Accordingly, based on this report by Walden et al. (2007),[1] it is possible to conclude that if patients took this particular OAD hydromorphone formulation orally together with a beverage containing 20−40% ethanol, there is a clear safety risk.

Sathyan G et al. in 2008 reported that there was only a minor effect on the single-dose plasma pharmacokinetics (small increase in Cmax) of hydromorphone after concomitant oral intake of a controlled release OROS formulation of hydromorphone together with ethanol at 4%, 20% or 40% in orange juice.[67] Based on the experience of an OAD hydromorphone formulation and the OROS controlled release formulation it is suggested that this ethanol−drug interaction is mainly related to properties of the dosage form rather than the active pharmaceutical ingredient per se, which in accordance with QbD drug development should be considered in any pharmaceutical formulation work.[3]

In an *in vitro* study reported by Traynor et al. in 2008, three different controlled release dosage forms with tramadol were differently affected by the presence of ethanol *in vitro*.[68] The most ethanol sensitive formulation had approximately 55% and 95% released *in vitro* within 2 h in 20% and 40% ethanol respectively. The authors suggested that alcohol-soluble excipients should not be included in controlled release formulations where dose dumping can lead to serious side-effects. Formulation properties were the major explanation why these three different controlled release products, with the same active substance, behaved differently *in vitro* at 20% and 40% ethanol. The most *in vitro* sensitive formulation was a multiparticulate formulation (in a capsule) with an ethanol soluble polymer in the pellet coating (large surface area).[68]

In another study, the aim was to determine the influence of ethanol on the *in vitro* release rate of verapamil from melt extruded tablets (Meltrex; form A) in contrast to three other direct compressed Verapamil sustained release formulations (forms B−D).[69] Form A (melt extruded) contained verapamil hydrochloride in a hydroxypropylcellulose and hypromellose matrix. Formulations B, C and D (sustained release) all contained verapamil hydrochloride in a natrium-alginate matrix (as a retarding agent). Ethanol had no effect on the *in vitro* dissolution profiles for Verapamil Meltrex at any concentrations between 5 and 40% ethanol. In contrast, the three formulations B, C and D had a significantly increased *in vitro* dissolution rate in 20 and 40% ethanol compared to water. An initial rapid release (within 2 h) was observed in 20% and 40% ethanol, with a mean *in vitro* dissolution of 99%.[69] The major part of the increased dissolution occurred between 1 and 2 h and was defined as a dose dumping. It is clear that this ethanol dependent absorption interaction is completely formulation dependent and should therefore be considered as an important factor in all formulation development. Roth et al. (2008) considered the widespread use and accessibility of ethanol as a major factor of concern for interactions between alcohol and drugs through both pharmacokinetic and pharmacodynamic mechanisms.[69]

Fadda et al. (2008) investigated the drug release from three controlled release monolithic and multiparticulate preparations of mesalazine.[70] They found that ethanol increased the drug release from mesalazine MR preparations *in vitro* to

(65) Vashi, V.; Harris, S.; El-Tahtawy, A.; Wu, D.; Cipriano, A. Clinical pharmacology and pharmacokinetics of once-daily hydromorphone hydrochloride extended-release capsules. *J. Clin. Pharmacol.* **2005**, *45*, 547–54.

(66) Kaiko, R. F.; Benziger, D. P.; Fitzmartin, R. D.; Burke, B. E.; Reder, R. F.; Goldenheim, P. D. Pharmacokinetic-pharmacodynamic relationships of controlled-release oxycodone. *Clin. Pharmacol. Ther.* **1996**, *59*, 52–61.

(67) Sathyan, G.; Sivakumar, K.; Thipphawong, J. Pharmacokinetic profile of a 24-h controlled-release OROS formulation of hydromorphone in the presence of alcohol. *Curr. Med. Res. Opin.* **2008**, *24*, 297–305.

(68) Traynor, M. J.; Brown, M. B.; Pannala, A.; Beck, P.; Martin, G. P. Influence of alcohol on the release of tramadol from 24-h controlled-release formulations during in vitro dissolution experiments. *Drug Dev. Ind. Pharm.* **2008**, *34*, 885–9.

(69) Roth, W.; Setnik, B.; Zietsch, M.; Burst, A.; Breitenbach, J.; Sellers, E.; Brennan, D. Ethanol effects on drug release from Verapamil Meltrex®, an innovative melt extruded formulation. *Int. J. Pharm.* **2009**, *368* (1−2), 72–5.

different degrees. They also concluded that there is a complex interplay between the formulation, the release medium and the duration to its ethanol exposure. Because of the poor understanding of the specific interaction today, it was suggested that it is not possible to predict the extent of impairment induced by ethanol on *in vitro* drug release.[70]

In another study by Henderson et al. in 2007 the plasma pharmacokinetics of carvedilol, taken orally as a single controlled release capsule (40 mg), was not affected by intake of 240 mL of a 20% alcoholic beverage (pure ethanol diluted with sugar free drink).[71] In the report the *in vitro* release of the drug was significantly affected by the presence of ethanol. For instance, at 2 h the *in vitro* release of carvedilol was 85% and 95% for 20% and 24% ethanol, respectively. This difference of ethanol sensitivity *in vitro* and *in vivo* is most likely explained by the relatively low dose of alcohol used *in vivo* (20% alcoholic beverage) and the protracted intake over time which will have minimized the concentration and volume of ethanol (240 mL was given as 4 × 60 mL portions taken over 30 min). In addition, the absence of an effect *in vivo* may also be explained by the fact that this study was performed in the fed state.

For the OAD hydromorphone formulation the interaction was clearly dependent on the alcohol concentration between 20% and 40% (mean plasma Cmax increased 1.9-fold and 5.5-fold), but the tmax occurred at approximately 1 h in both cases.[1] The study with an OAD hydromorphone formulation also pointed out that the mean value is probably less suitable to measure, since it was demonstrated that there was strong interindividual variability in gastrointestinal absorption of the drug in the response to alcohol. Therefore, it is advisible to investigate the effect of ethanol *in vivo* on an individual basis and to use a sufficiently and realistically large volume (probably 120 mL or more) of a strong alcoholic beverage (40%).

A single-dose study *in vivo* with an extended release oral dosage form of morphine (100 mg, KADIAN) was not affected by concomitant intake of 240 mL of 40% alcohol (4 × 60 mL shots) in the fasted or fed state.[72] There were no *in vitro* data reported in this study. The major explanation for the absence of an ethanol effect on the *in vivo* absorption reported in this study was suggested to be the composition of the pH-independent and pH-dependent water-soluble polymers interspersed within a water-insoluble polymer matrix.[72] The observation is not explained by rapid gastric absorption of ethanol since there is limited absorption direct from the stomach.[51,52] However, since this was a single-dose study in healthy subjects, gastric emptying was not prolonged by the effect of other drugs, age, posture and/or disease(s), which are very common for treatment situations in many patients.

It has been reported that the *in vitro* dissolution data of oxycodone from Oxycodon HCl STADA PR tablets (which formulation is marketed within Europe, also under other trade names) was clearly dependent on the presence of the ethanol concentration in the *in vitro* dissolution media [Smith et al. (2007)[83]]. The *in vitro* release of oxycodone had a lag period between 0 and 30 min, but between 30 and 60 min a major part of the dosage form was released when the ethanol concentrations in the dissolution media were higher than 24%. The most plausible explanation is that the dosage form has lost its controlled release function with the consequence that almost the entire dose is released at once. In this case, the *in vitro* release was >75% and >90% at 1 and 2 h respectively in the ethanol concentration interval 28%−40% [Smith et al. (2007);[83] Leuner et al. (2007)[84]]. It takes some time for the major part of the active drug to be dissolved from the controlled release dosage form. This is because there is a time factor in the degradation of controlled release properties as described also in other reports.[69] It is clear that ethanol sensitive formulations with significant *in vitro* dose dumping, such as this one discussed here, will most likely lead to *in vivo* dose dumping [i.e., increased maximal plasma exposure (Cmax) and shorter time to tmax] at higher ethanol concentrations in patients to a varying degree. There is a large intra- and interindividual variability in gastric retention and emptying time as discussed above.[18,73−75] It is expected that the *in vivo* dissolution rate of oxycodone from an ethanol sensitive controlled release formulation in the stomach will be highly dependent on the total volume of ethanol ingested, its dilution in the stomach, the fasted or fed state of the individual, gastric mixing and gastric residence time.

Based on the discussion above it is clear that in some patients more or less the whole of the dose of an ethanol sensitive controlled release formulation (such as the one discussed above) will be dissolved in the stomach and then—once the gastric emptying commences after various lag periods—quite rapidly emptied into the small intestine where the absorption takes place (dose dumping). For instance, the Cmax and tmax of oxycodone after oral intake as a controlled-release formulation and as a solution are significantly different: the tmax of the solution occurred at

(70) Fadda, H. M.; Mohamed, M. A.; Basit, A. W. Impairment of the in vitro drug release behaviour of oral modified release preparations in the presence of alcohol. *Int. J. Pharm.* **2008**, *360*, 171–6.
(71) Henderson, L. S.; Tenero, D. M.; Campanile, A. M.; Baidoo, C. A.; Danoff, T. M. Ethanol does not alter the pharmacokinetic profile of the controlled-release formulation of carvedilol. *J. Clin. Pharmacol.* **2007**, *47*, 1358–65.
(72) Johnson, F.; Wagner, G.; Sun, S.; Stauffer, J. Effect of concomitant ingestion of alcohol on the in vivo pharmacokinetics of KADIAN (morphine sulfate extended-release) capsules. *J. Pain* **2008**, *9*, 330–6.
(73) Coupe, A. J.; Davis, S. S.; Evans, D. F.; Wilding, I. R. Correlation of the gastric emptying of nondisintegrating tablets with gastrointestinal motility. *Pharm. Res.* **1991**, *8*, 1281–5.
(74) Coupe, A. J.; Davis, S. S.; Wilding, I. R. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. *Pharm. Res.* **1991**, *8*, 360–4.
(75) Langguth, P.; Lee, K. M.; Spahn-Langguth, H.; Amidon, G. L. Variable gastric emptying and discontinuities in drug absorption profiles: dependence of rates and extent of cimetidine absorption on motility phase and pH. *Biopharm. Drug Dispos.* **1994**, *15*, 719–46.

1 h compared to at least 3−4 h for the controlled release tablet.[76] The Cmax of oxycodone based on dose correction and single dose was found to be at least 4-fold higher after orally dosing a solution of oxycodone.[76] This intentional difference between a solution and controlled release formulation of oxycodone indicates that if the controlled release formulation is completely dissolved in the stomach (as a consequence of the destruction of the controlled release mechanism), the plasma profile will almost certainly mimic the plasma concentration−time profile obtained after oral administration of a solution and not the controlled release formulation.[76]

Although the key factor of the pharmacokinetic ethanol−drug (dose dumping) interaction is the product formulation, the significance of the enhancing effect of ethanol on drug intestinal permeability has not yet been thoroughly investigated. Oxycodone hydrochloride is a drug that is classified as soluble, it is a weak basic drug with a pK_a value of 8.9, an intermediate lipophilicity and the octanol:buffer distribution coefficient is 1.64 at 37 °C and pH 7.4.[77−79] These physicochemical properties and previous data predict that the drug will be rapidly absorbed (amount/time) when it has been emptied into the small intestine, which also is confirmed with only about 1 h to reach tmax when given orally as a solution.[76] Since oxycodone hydrochloride has a solubility of 100 mg/mL, the concentration gradient locally in the upper small intestine is expected to be high for some individuals. In a recent Caco-2 cell transport experiment it was found that the *in vitro* permeability (Papp) was similar to that of metoprolol, which is classified as a high permeability drug.[2,77,80] Amidon et al. (1995)[2] suggests that oxycodone is classified as class I drug (high intestinal permeability; high solubility) according to the biopharmaceutical classification system (BCS). Indeed, many drugs that are formulated in controlled release dosage formulations belong to BCS class I and II.[81,82] For this specific interaction between ethanol and a modified release formulation, it means that, once the drug is completely dissolved by ethanol, it will be rapidly absorbed as the intestinal permeability is high and even more increased by the presence of ethanol. In addition, the predicted significant concentration gradient across the intestinal epithelial membrane will ensure a rapid intestinal absorption (amount/time), short time to tmax and very high plasma concentrations of the active drug. Typically, peak oxycodone plasma concentrations are attained within 1 h of ingestion of a conventional solution, confirming that, once in solution, the absorption of oxycodone is rapid.[76] In this Caco-2 study it was also shown that the Papp value increased when the ethanol concentration increased from 0 to 5%.[80] Accordingly, it may be speculated that, when ethanol is present in the intestinal lumen, it may enhance the drug permeability in the upper region of the small intestine by the presence of ethanol. The direct enhancing effect of ethanol on the intestinal barrier has been shown by using an *in vivo* single-pass perfusion in humans.[50] For this specific interaction, it means that ethanol can have two effects on the absorption rate: to completely dissolve the modified release dosage formulation and to enhance the small intestinal permeability.

Conclusion

When ethanol interacts with a controlled release product, such that the controlled release mechanism is impaired, the delivery of the dissolved drug into the small intestine and the consequent absorption may result in high plasma concentrations outside the individual safe therapeutic range. Thus, an absorption ethanol−drug interaction is a very serious safety concern when substantially the entire dose from a controlled release product is rapidly emptied into the small intestine in an uncontrolled manner (dose dumping), having been largely dissolved in a strong alcohol beverage in the stomach during a sufficient lag-time in gastric emptying.

Based on the literature, a two hour time frame for screening the *in vitro* dissolution profile of a controlled release product in ethanol concentrations of up to 40% is

(76) Benziger, D. P.; Kaiko, R. F.; Miotto, J. B.; Fitzmartin, R. D.; Reder, R. F.; Chasin, M. Differential effects of food on the bioavailability of controlled-release oxycodone tablets and immediate-release oxycodone solution. *J. Pharm. Sci.* **1996**, *85*, 407–10.

(77) Kasim, N. A.; Whitehouse, M.; Ramachandran, C.; Bermejo, M.; Lennernas, H.; Hussain, A. S.; Junginger, H. E.; Stavchansky, S. A.; Midha, K. K.; Shah, V. P.; Amidon, G. L. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol. Pharmaceutics* **2004**, *1*, 85–96.

(78) Poyhia, R.; Seppala, T. Liposolubility and protein binding of oxycodone in vitro. *Pharmacol. Toxicol.* **1994**, *74*, 23–7.

(79) Plummer, J. L.; Cmielewski, P. L.; Reynolds, G. D.; Gourlay, G. K.; Cherry, D. A. Influence of polarity on dose-response relationships of intrathecal opioids in rats. *Pain* **1990**, *40*, 339–47.

(80) Volpe, D. A.; Asafu-Adjaye, E. B.; Ellison, C. D.; Doddapaneni, S.; Uppoor, R. S.; Khan, M. A. Effect of ethanol on opioid drug permeability through caco-2 cell monolayers. *AAPS J.* **2008**, *10*, 360–2.

(81) Knutson, T.; Fridblom, P.; Ahlström, H.; Magnusson, A.; Tannergren, C.; Lennernäs, H. Increased Understanding of Intestinal Drug Permeability Determined by the LOC-I-GUT Approach Using Multislice Computed Tomography. *Mol. Pharmaceutics* **2009**, *6* (1), 2–10.

(82) Tannergren, C.; Bergendal, A.; Lennernas, H.; Abrahamsson, B. Toward an increased understanding of the barriers to colonic drug absorption in humans: implications for early controlled release candidate assessment. *Mol. Pharmaceutics* **2009**, *6*, 60–73.

(83) Smith, K. J.; Prater, D. A.; Leuner, C.; Walden, M.; Reimer, K. The Potential and Significance of the Interaction of Ethanol with Oral Prolonged Opioid Products. World Congress, World Institute of Pain, Budapest, Hungary, September 25−28, 2007; Poster Number 2108.

(84) Leuner, C.; Prater, D. A.; Scherer, S.; Topham, T. E.; Walden, M. Predictability of the Potential for Ethanol Related Dose Dumping in Oral Prolonged Release Opioid Formulations. AAPS Annual Meeting & Exposition, San Diego, CA, Nov 11−15, 2007.

strongly supported as physiologically and pharmacologically relevant and may be considered as the absolute minimum standard. It is also evident from the recent literature that the dilution, absorption and metabolism of ethanol in the stomach are processes with a minor effect on the local ethanol concentration and that ethanol exposure will be highly dependent on the volume and ethanol concentration of the fluid ingested and the rate of intake and gastric emptying. It is also important to realize that there are no final *in vitro* tests validated and the present *in vitro* methods need to be correlated to *in vivo* clinical pharmacokinetic studies.

When and in which patients a clinically significant dose dumping will happen is almost impossible to predict and will depend on drinking behavior and the highly variable gastrointestinal factors of importance for dissolution, transit and absorption. Therefore, controlled release products which show a vulnerability to ethanol during two hours *in vitro* should not be marketed unless they have been shown to be clinically safe through *in vivo* testing with alcoholic beverages of up to 40% ethanol. Alternatively, such preparations should be reformulated in accordance with QbD principles.

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