What is “fasting” drug administration?
On the role of gastric motility in drug absorption

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Drug intake on an empty stomach usually is regarded as fasting administration. However the fasting state has recently been defined not so much in terms of the stomach contents but rather in terms of gastric motor function. The motor activity of the stomach is a major factor controlling the delivery of an active compound to the site of absorption in the small intestine. Advances in understanding gastric motility, therefore, should be introduced into pharmacological concepts. There are two major issues deserving special attention: first, gastric motility is characterized by two distinct and quite different patterns - the fasting (interdigestive) and the fed (digestive) patterns. Fasting motor function appears to be the prevailing type of motor action, being interrupted for the time required to digest and transport the chyme to the duodenum, and thereafter being restored. Second, to some extent liquids and solids can leave the stomach independently of each other, because their removal is related to different anatomical areas of the stomach. Liquid emptying is attributed to the “proximal stomach”, whereas solid emptying is mainly a function of the “distal stomach”. This differentiation is important for drug absorption, because therapeutic agents generally cannot be administered on their own, but need to be supplied in various dosage forms which exhibit different physical properties.

The fasting motility of the distal stomach consists of a typical cyclical process with an average cycle length of about 2 h. Each cycle can be divided into three (or four) phases. During phases 1 and 2 there is no relevant transport activity; only during phase 3, which is no longer than about 5 to 15 minutes, large solid particles are emptied from the stomach into the duodenum by propulsive contraction waves [1-3]. This implies that the fasting pattern of gastric motility can be maintained even if the stomach is not empty, provided that the intake of liquids and solids is restricted to non-nutritive materials, such as water, saline or the metal markers used to measure gastric emptying. Depending on the time interval between ingestion and the occurrence of phase 3 contractions, the gastric residence time of non-nutritive solids in the fasting state varies between a few minutes and 2–3 h [4, 5]. If non-degradable solids larger than 1–2 mm, possibly with a distinct threshold at 1.4 mm, are supplied with a meal, these particles do not leave the stomach during the digestive period; they require resumption of fasting motility in order to be removed by a propulsive phase 3 contraction [6-8].

The fact that emptying of large indigestible solids cannot be achieved during digestion, but is a typical function of the “fasting stomach”, emphasizes the need to define “fasting” according to motility rather than to stomach contents.

In contrast, liquid emptying is primarily related to the gastroduodenal pressure gradient, which is generated by the proximal stomach [1, 2]. Non-nutritive liquids, such as water and saline, may leave the stomach at almost any time. Initially emptying is very rapid and than it slows, thereby approximating an exponential function [9-11]. Liquids containing nutrients, like glucose, amino acids, fatty acids, or nutrient mixtures, exhibit a lower rate of transport to the duodenum [9, 10]. It is important to recognize that liquid food, such as solutions of carbohydrates, protein hydrolysates, fatty acids or mixtures of any of them, interrupt the fasting motility of the distal stomach [3], and thus influence the gastric residence time of co-ingested solids.

Gastric handling of a drug, whether a particular dosage form or an active ingredient, is governed by the stomach function following ingestion, so it is gastric motility after medication that controls absorption of the therapeutic agent, not the fact that the stomach is empty prior to drug intake. During the interdigestive period fasting motility can be maintained when pharmaceutical products are administered with water. When an immediate release formulation of a highly soluble compound, such as paracetamol, is ingested with water, gastric emptying of the aqueous drug solution and absorption of the active compound is very rapid; this is shown by the very short
time required to reach the maximum plasma concentra-
tion, which may be less than 20 min [12]. When healthy
young males received an aqueous solution of antipyrine
and caffeine, the time to the peak concentrations was
equally short for both compounds, and was found to be
very uniform (15 min in 9 of 10 subjects), whereas in a
comparable group of females $t_{\text{max}}$ ranged up to 2 h, even
though all of them had received the same combination on
an empty stomach (Walter-Sack et al., unpublished). The
differences in females are likely to be attributable to vari-
atation in gastric emptying related to the menstrual cycle,
even though the hormonal effect on liquid emptying has
been considered to be minor [13]. Data on the absorption
of sodium salicylate administered as an aqueous solution
support the concept that gastric emptying of a liquid
varies significantly with the menstrual cycle [14]. When a
conventional acetylsalicylic acid tablet was given with
water, the plasma concentrations of salicylic acid rose
quite rapidly, suggesting fast delivery of the active ingre-
dient to the small intestine [15]. Using enteric coated gra-
nules, the plasma concentrations of salicylic acid were
found to rise more slowly, but without an appreciable lag
time. This is compatible with a granule size sufficiently
small not to require a phase 3 contraction for removal
from the stomach. When an enteric coated tablet was
given which would not decompose within the stomach,
and therefore did require a phase 3 contraction for trans-
port of the intact dosage form to the duodenum, the plas-
ma drug level only started to rise after a lag time of more
than 1 h in 7 of 8 individuals, indicating that the interval
between drug ingestion and the occurrence of a phase 3
contraction in these subjects exceeded 1 h [15]. Thus, the
pattern of drug absorption differed, even though each
acetylsalicylic acid preparation had been taken on an
empty stomach and with water alone, thus maintaining
fasting gastric motility and thereby providing qualified
fasting conditions. There is further evidence that the
absorption of an active compound reflects a specific in-
teraction between a given dosage form and fasting gastric
motility [16, 17].

Pharmaceutical products may be congested with a
Heidelberg capsule, an electronic device used to assess the
time of a phase 3 activity by indicating an immediate rise
in the intraluminal pH [4, 18]; this will not disrupt fasting
motility, and therefore it can be regarded as fasting drug
administration, even though the stomach contains solid
material in addition to the medication. These examples
show that it is no longer adequate to define \textit{fasting drug
administration} as intake on an empty stomach; rather it
should be described as \textit{drug intake whilst maintaining fast-
ing gastric motility} [17, 19].

The minimum quantity of nutrients required to induce
the digestive pattern of motility is not known. However
the “food effect” is not restricted to regular meals; any
kind of liquid containing nutrients, for instance maltose or
fatty acids, will convert gastric motor function to the fed
pattern [3]. Therefore, the effect of a beverage, or of a
solid or solid-liquid meal, will only differ quantitatively
but not qualitatively, i.e. the duration of the digestive peri-
od will vary. Consequently, drug intake with any kind of
beverage, such as fruit juice, cannot be regarded as fasting

drug administration, and so it is no longer a valid reference
procedure to assess the effect of a meal. In order to assure
fasting gastric motility at the time of medication in healthy
individuals, it may be sufficient to abstain from food in-
take for about 12 h, unless the last meal was very heavy.
This is likely to differ in subjects with delayed gastric
emptying due to an underlying disease, such as diabetic
gastroparesis, or on comedication with a drug affecting
gastric motor activity. Gastric motor function should re-
cieve special attention in therapeutic trials, but it is not
only important in experimental drug investigations. To
achieve fasting drug administration in everyday manage-
ment of patients is a complex issue; for instance, patients
taking drugs several times a day may also have to stick to a
certain dietary regimen, such as eating frequent small
meals because of diabetes mellitus, gastrointestinal dis-
orders, or loss of appetite in malignant disease. Some of
these patients will only be adequately managed by taking
into account the role of gastric motility both in drug treat-
ment and dietary recommendations.

\begin{thebibliography}{99}
\bibitem{1} Lübke HJ, Wienbeck M (1985) Gastrointestinale Motilität und
interale Resorption beeinflussen sich gegenseitig. Klinikarzt 14:
25–36
\bibitem{2} Minami H, McCallum RW (1984) The physiology and pathophysi-
ology of gastric emptying in humans. Gastroenterol 86: 1592–
1610
\bibitem{3} Rees WDM, Malagelada JR, Miller LJ, Go VLW (1982) Human
interdigestive and postprandial gastrointestinal motor and
\bibitem{4} Ewe K, Press AG, Dederer W (1989) Gastrointestinal transit of
undigestible solids measured by metal detector EAS II. Eur J
Clin Invest 19: 291–297
\bibitem{5} Park HM, Chernish SM, Rosenek BD, Brunell RL, Hargrove B,
Dig Dis Sci 29: 207–212
\bibitem{6} Feldman M, Smith HJ, Simon TR (1984) Gastric emptying of
solid radiopaque markers: Studies in healthy subjects and
diabetic patients. Gastroenterol 87: 895–902
\bibitem{7} Meyer JH, Elashoff J, Porter-Fink V, Dressman J, Amidon GL
(1988) Human postprandial gastric emptying of 1–3-millimeter-
spheres. Gastroenterol 94: 1315–1325
\bibitem{8} Smith HJ, Feldman M (1986) Influence of food and marker
length on gastric emptying of indigestible radiopaque markers in
healthy humans. Gastroenterol 91: 1452–1455
\bibitem{9} Bury KD, Jambunathan G (1974) Effects of elemental diets on
gastric emptying and gastric secretion in man. Am J Surg 127:
59–64
\bibitem{10} Dooley CP, Reznick JB, Valenzuela JE (1984) Variations in gas-
tric and duodenal motility during gastric emptying of liquid
meals in humans. Gastroenterol 87: 1114–1119
\bibitem{11} Smith JL, Jiang CL, Hunt JN (1984) Intrinsie emptying pattern of
\bibitem{12} Walter-Sack I, Luckow V, Gucerle R, Weber E (1989) Unter-
suchungen der relativen Bioverfügbarkeit von Paracetamol
nach Gabe von festen und flüssigen oralen Zubereitungen sowie
rektalen Applikationsformen. Arzneim Forsch/Drug Res 39:
719–724
\bibitem{13} Gill RC, Murphy PD, Hooper HR, Bowes KL, Kingma YJ
(1987) Effect of the menstrual cycle on gastric emptying. Disge-
ston 36: 168–174
\bibitem{14} Minkiewicz SL, Shively CA, Vesell ES (1982) Sex differences in
absorption kinetics of sodium salicylate. Clin Pharmacol Ther 31:
30–37
\end{thebibliography}