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Research Article

ASIAN FOOD (CARBOHYDRATE, PROTEIN, FAT) INCREASE SIMVASTATIN BIOAVAILABILITY ESPECIALLY IN MALAYSIAN SUBJECTS

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ABSTRACT

Simvastatin 40 mg tablet was evaluated with Malaysian food in 9 healthy Malaysian male volunteers in a randomized, single dose, two-way crossover study. Simvastatin with Malaysian food produced higher AUC_{0-24}, C_{max} and T_{max} values, as compared with fasting condition. The K_e, $t_{1/2}$ and Cl did not show any significant difference between fasting and food conditions. However, food delayed gastric emptying and gastrointestinal transit, the longer gastric residence time of the simvastatin is offset by the rise in the pH of gastrointestinal tract. Food may be did not affect the increase of splanchnic hepatic blood flow by decreasing first pass metabolism of simvastatin. Food may be had the effect on the increasing of pH of gastrointestinal tract which lead to increase the stability of simvastatin in gastrointestinal fluid and its absorption into blood circulation.

Keywords: Asian food, simvastatin bioavailability

INTRODUCTION

There are two distinct gastrointestinal motility patterns, fasted and fed, in human and animals which consume food on a discrete basis [1]. Motility and secretory patterns in fasted and fed states are quite different [2]. As a result, bioavailability of orally administered drugs may differ depending on whether the medications are given in the presence or absence of food.

The motility pattern in the fasted state, commonly called the migrating motor complex (MMC), is organized into alternating cycles of activity and quiescent and can be subdivided into basal, preburst and burst intervals [1,3]. However, current research in gastric motility and transit distinguishes two separate states: the fed mode and the fasting mode. The fed mode commences when food enters the stomach. It is characterized by continuous contractile activity which gives rise to the grinding of food particles, emptying, when these reach a liquid consistency and retropulsion back into the stomach to effect further size reduction. Indigestible solids are held back in the stomach. The fasting mode consists of a period of limited activity which gradually increases to a period of intense contractions, the migrating motor complex, which sweeps the fasting contents out of the stomach and migrates down the intestine. This is sometimes called the housekeeper effect [4].

Simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, is administered in the form of lactone prodrug. The lactone ring is hydrolyzed *in vivo* to produce the hydroxyl acid derivatives which are the pharmacologically active forms of this drug, and this is believed to take place predominantly in the liver [5-6].

Thus, the study presented herein is to determine the rate and extent of simvastatin form prodrug absorption under the changed pH of stomach fluids in fasting condition to non-fasting by food.

METHODS

Subjects and study design

Nine healthy Malaysian male volunteers nonsmoking participated in this study were consenting healthy males between ages of 22 and 49 years. The study protocol of oral single dose 40 mg simvastatin following guidelines of the Helsinki Declaration of 1975 and its amendments was approved by the Ethics Committee of the joint Pinang Hospital/School of Pharmaceutical Sciences, Universiti Sains Malaysia Committee on Bioavailability Studies. Written informed consent was obtained from each subject. The volunteers were informed that they could withdraw from the study any time. The physical examinations, blood chemistries, hematology and urinalysis of volunteers were in the normal range. The volunteers were instructed not to take any other medication for two week prior to and during the study.

Nine volunteers were randomized in two blocks. They were stay at the study center 2 hours before to 24 hours after dosing. After eating a light snack before 11:00 p.m., they were fasted overnight. For two study groups, subjects received orally single dose of 40 mg tablet of simvastatin. For safety reasons, there was an interval of one week between the two study groups to allow simvastatin free days between the study days. In first group, the fasting volunteers were given a single dose of 40 mg tablet of simvastatin at 8.00 a.m., with 200 mL of water after 10-hour overnight fast. In the second group, the volunteers were consumed the standard local food (180 gm chicken "satay" and 200 gm rice "ketupat"). The meal provided an estimated 60.00 gm carbohydrate, 34.90 gm protein and 30.70 gm fat (656 kcal). The meal is provided with 200 mL of water. Duration for food consumed 20 min then immediately the volunteers were given a single dose of 40 mg tablet simvastatin with 50 mL of water. Blood samples were drawn 10 mL into a labeled glass tubes immediately before administration of simvastatin and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration. The plasma was isolate from whole blood by centrifugation at 3000 rpm for 15min and then transferred into a glass tube, placed in a freezer -20^{0}C until frozen, and then stored in a -85^{0}C freezer until analysis.

Sample analysis

LC-MS-MS method was validated at Unversiti Sains Malaysia and Centre for Drug Research. Serum samples containing simvastatin were quantified by liquid chromatography tandem mass spectrometry (LC-MS-MS). The simvastatin was extracted from serum using ethyl acetate and hexane (90/10%, v/v) by using lovastatin as internal standard. The solutes were separated on a Symmetry C_{18} column with mobile phase consisting of mixture of acetonitrile and 3 mM formic acid (75/25%, v/v) at flow rate 500 µL/min. For quantitation in the selective reaction monitoring (SRM) in positive ion mode, the daughter ions m/z 325 for simvastatin and m/z 285 for lovastatin were used. Parent ions in positive ion mode were m/z 441.3 for simvastatin and m/z 405.1 for lovastatin. The lower limit of quantitation of 0.25 ng/mL was achieved. The within

day coefficient of variations were less than 14.00% and the accuracies were between 90.00 and 109.33%. The day-to-day coefficients of variation were less than 10.00% and accuracies were between 97.70 and 106.60%.

Pharmacokinetic Analysis

The pharmacokinetics of simvastatin was characterized by peak concentrations in serum (C_{max}), concentration peak time (T_{max}), elimination rate K_e, elimination half-life ($t_{1/2}$), clearance (Cl), volume of distribution (V_d) and areas under the drug serum concentration-time curve up to 24 hours (AUC_{0-24}).

Statistical Analysis

The data are expressed as mean values ± SD. Data were analyzed by Student t test comparing fasting and food conditions for each volunteer. In the case of $T_{max,}$ by the Wilcoxon test. The statistical program SPSS for Windows, version 11.5 will use for the analysis. Differences were considered statistically significant when $p < 0.05$.

RESULTS

Biodata of nine volunteers and pharmacokinetics parameters of simvastatin in nine volunteers after 40 mg oral simvastatin in fasting, food conditions were shown in Table 1 and Table 2. Figure 1 shows the mean serum levels of simvastatin in both conditions.

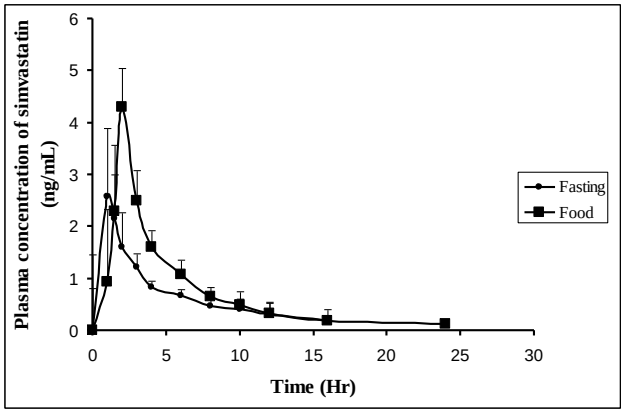

Figure1:The mean plasma concentration versus time plot for simvastatin with fasting and food. Mean ± SD, N=9

Table1: Biodata of nine healthy volunteers

Volunteer	Age (year)	Weight (kg)	Height (cm)	Body Mass Index (BMI)
V1	49	58	163	21.8
V2	40	55	165	20.2
V3	22	67	169	23.5
V4	33	70	162	26.7
V5	24	85	167	30.5
V6	23	64	170	22.2
V7	22	67	170	23.2
V8	31	78	179	24.3
V9	34	70	163	26.4
Mean	30.89	68.22	167.56	24.31
± SD	9.31	9.24	5.29	3.12

The concomitant intake of simvastatin with meal provided an estimated 60.00 gm carbohydrate, 34.90 gm protein, and 30.70 gm fat (656 kcal). This resulted was considerable and significant higher AUC_{0-24} and C_{max} values for simvastatin as compared with the ingestion of the simvastatin on an empty stomach.

In each volunteer, the AUC was larger when simvastatin was taken together with the food than when it was taken on an empty stomach. For both (fasting and food) conditions, the interindividual variation was considerable with respect to AUC_{0-24} value. For simvastatin the AUC_{0-24} ranged from 6.20 to 15.86 ng.mL^{-1}hr in fasting state and from 12.56 to 23.86 ng mL^{-1}hr in food state. However, when simvastatin taken with food, the mean (± SD) AUC_{0-24} of the simvastatin increased from 10.90 ± 3.21 (fasting state) to 16.23 ± 3.29 ng .mL^{-1} .hr. ($p < 0.05$) the AUC_{0-24} increased with food 50% higher than fasting.

When the fasting and fed data within each volunteer were compared, it was seen that the peak concentrations (C_{max}) values of simvastatin were higher in 8 of the 9 volunteers in the fed state. For both (fasting and food) conditions, the interindividual variation was considerable with respect to peak concentration value. For simvastatin, the peak concentration ranged from 0.93 to 4.96 ng/mL during fasting condition and from 3.12 to 6.34 ng/mL in the food state. When simvastatin taken with food, the mean (± SD) C_{max} of the simvastatin increased from 2.61 ± 1.42 (fasting state) to 4.22 ± 1.32 ng/mL ($p < 0.05$) the C_{max} increased with food 85% higher than fasting state.

Table 2 Pharmacokinetic parameters of simvastatin in nine volunteers after 40 mg oral simvastatin in fasting and food conditions

	AUC_{0-24} ng.mL^{-1}.hr		C_{max} (ng/mL)		T_{max} (hr)		$t_{1/2}$ (hr)		K_e (/hr)		V_d (L/Kg)		Cl (L/hr)	
Subject	**F**	**N**	**F**	**N**	**F**	**N**	**F**	**N**	**F**	**N**	**F**	**N**	**F**	**N**
1	15.86	23.86	2.13	3.12	1.00	2	4.30	3.93	0.16	0.18	223	144	36	25
2	6.20	15.31	1.23	3.35	1.00	4	2.20	1.55	0.30	0.45	335	102	106	46
3	8.95	16.34	0.93	6.34	3.00	2	6.50	2.90	0.11	0.24	464	142	50	34
4	12.70	13.10	3.90	4.73	1.00	3	1.14	2.04	0.61	0.34	71	118	43	40
5	10.93	17.90	1.90	5.90	1.00	1.5	3.93	2.04	0.18	0.34	195	74	34	25
6	6.97	12.56	1.86	3.20	1.00	1.5	3.10	2.98	0.23	0.23	342	199	77	46
7	10.40	15.70	2.33	2.89	1.00	1.5	3.80	3.03	0.18	0.23	260	154	48	35
8	14.40	16.13	4.28	5.10	2.00	4	1.48	1.83	0.47	0.38	72	79	34	30
9	11.70	15.20	4.96	3.33	1.00	1.5	1.97	2.09	0.35	0.33	131	108	46	36
Mean	10.90	16.23	2.61	4.22	1.33	2.33	3.16	2.49	0.29	0.30	233	124	53	35
± SD	3.21	3.29	1.42	1.32	0.71	1.06	1.68	0.80	0.16	0.09	132	40	24	8
P	0.003		0.016		0.016		0.293		0.831		0.032		0.055	

F, fasting; N, non-fasting

The mean observed T_{max} for simvastatin with food is considerable and significant higher than when simvastatin is taken on an empty stomach. However, food intake delayed the absorption of simvastatin which is reflected both by a delay in T_{max} as well as an increase in the number of people with a more prolonged lag time prior to the appearance of measurable concentrations of simvastatin in blood. The mean (± SD) T_{max} of the simvastatin increased from 1.33 hr ± 0.71 (fasting state) to 2.33 hr ± 1.06 (food state) ($p < 0.05$) the increased with food 90% higher than fasting state.

The half-life obtained in this study was not influenced by food. However, mean observed $t_{1/2}$ determined for simvastatin did not show any significant difference between fasting and fed states: 3.16 ± 1.68 and 2.49 ± 0.80 hours, respectively ($p > 0.05$).

The mean observed K_e (elimination rate) determined for simvastatin did not show any significant difference between fasting and fed states: 0.29 ± 0.16 and 0.30 ± 0.09/hour, respectively ($p > 0.05$).

The mean observed V_d (volume distribution) determined for simvastatin did not show any significant difference between fasting and fed states: 232.57 ± 132.54 and 124.49 ± 39.76 L/Kg, respectively ($p > 0.05$).

The mean observed Cl (clearance) determined for simvastatin did not show any significant difference between fasting and fed states: 52.59 ± 23.87 and 35.29 ± 7.82 L/hr, respectively ($p > 0.05$).

DISCUSSION

Generally, an orally administered drug must be absorbed from the gastrointestinal tract to an extent and at a rate that will result in circulating drug levels sufficient to elicit a pharmacological response of desired magnitude and duration. The efficiency with which a drug is absorbed is a function of many variables. A drug product has to be sufficiently water soluble to dissolve in gastric and intestinal fluids, or both, and yet for passively absorbed compounds it must be able to diffuse across the lipoidal epithelial lining of the gastrointestinal tract into the systemic circulation. An acid labile drug has to be protected so that extensive degradation does not occur in gastric fluids and a drug that irritates the gastrointestinal mucosa has to be formulated so that the irritant effect is prevented or minimized [9].

For many oral administered medications, the presence of food affects pharmacokinetics [10]. However, the drug absorption kinetics from the gastrointestinal tract is influenced by a combination of physiological factors and biopharmaceutical properties such as gastrointestinal motility and permeability [11].

Moreover, food can influence the absorption, metabolism and elimination of drugs by complex mechanisms [10]. Food may decrease the bioavailability of certain drugs by forming a mechanical barrier on the gut wall or by physical binding between drug molecules and food constituents [12].

In addition, the food has an effect on gastric emptying, gastrointestinal motility, splanchnic blood flow and gastrointestinal secretions [9]. Dietary components, especially fat increase the secretion of bile which enhances the absorption of lipid soluble compounds. Therefore, the effect of food might be a result of interaction between food induced physiologic changes in the gastrointestinal tract and formulation factors influencing the rate of dissolution.

Physiologic changes, increased bile production which of particular importance for poor water soluble drugs, as it results in substantial concentrations of bile salts and lecithin that are known to be capable of facilitating the dissolution process through their wetting action and micellar solubilization [13]. In a fasting state, bile salt concentration in the proximal small intestine is about 3 to 5 mM. After food ingestion, bile output and luminal concentrations of bile components peak within 30 minutes with a peak level averaging about 15 mM in the proximal small intestine [14].

In general, most a lipophilic drug such as diazepam [15], spironolactoe [16-17], propranolol and metoprolol [18], isotretinoin [19] and amiodarone [20] had been shown to be solubilized in this way, and the apparent of absorption rate was increased. However, a similar mechanism may be explaining the observed increased absorption of simvastatin in this study after intake with the 30.70 gm fat-containing food.

Another prediction may the rate and extent of absorption of simvastatin increase in the presence of food. This is thought to be due to increased drug solubility, increased lymphatic absorption and prolonged residence time in the gastrointestinal tract [21].

In general, food ingestion increases splanchnic blood flow, and therefore the first-pass hepatic clearance of the drugs with high hepatic extraction ratio may decrease [22-23].

Simvastatin is known to have a very high degree of first-pass metabolism [24]. The results from the current study indicate that systemic exposure (C_{max} and AUC) to simvastatin is higher when administered with food rather than under fasting conditions. The difference in mean AUC values between fed and fasting conditions in this study is similar to the findings of studies conducted by Melander *et al* (1977); Colburn *et al* (1983); Overdiek and Merkus, (1986); Fabre and Timmer, (2003) when they concluded that food increase drugs absorption when drugs are immediately taken after food due to change in hepatic blood flow during the first passage through the liver and suggest that the amount of unchanged drug reaching systemic circulation is enhanced in the presence of food, possibly because the resultant increase in hepatic blood flow could lead to a reduction in first pass metabolism of drugs that have a high hepatic extraction ratio, such as spironolactone, propranolol, metoprolol, isotretinoin and gepirone.

Generally, food may markedly reduce pre-systemic clearance of (certain) lipophilic basic drugs via transient, complex effects on splanchnic hepatic blood flow, or shunt processes, resulting in an enhanced systemic availability of these drugs. A finding that is not observed in this current study. However, if food induces a higher gastrointestinal absorption of simvastatin, more substrate to pre-systemic clearance sites will be offered. This can explain the observed decreased first-pass metabolism of simvastatin which results in an increased of the systemic clearance (Cl) and the volume of distribution (V_d). However, in this current study, there was no difference between fasting and food Cl and V_d. A relative decrease in first-pass metabolism can also occur, as a result of food enhanced absorption of simvastatin, when the saturation of enzymes responsible for simvastatin biotransformation to take place.

There is another explanation is that the delay in gastric emptying and gastrointestinal transit may be caused by 60.00 gm carbohydrate containing food, or a change in gastric pH by 34.90 gm protein and 30.7 gm fat containing food, which allow a more complete dissolution or prolonged residence of simvastatin at a site in the proximal part of intestine from which absorption is optimum [26-27]. In addition to our results in this study, the differences in T_{max} in fasting and food states for the simvastatin may not be due to the food that may decrease first-pass metabolism of simvastatin by enhancing its rate of absorption. It may be due to the delay in gastric emptying and gastrointestinal transit by food and the longer gastric residence time of the simvastatin is offset by the rise in the pH of gastrointestinal tract [7-8].

Our results is consistent to other researchers maintains that food increases drugs absorption when it is administered following a food. They concluded that food increases drugs residence time in stomach and improves dissolution of the drugs by delaying gastric emptying. For example a study conducted by Welling *et al* (1976) found that food increases absorption of propoxphene and norpropoxyphene in 6 volunteers. Beermann and Grind (1978) found that food increases absorption of hydrochlorothiazide on 8 volunteers. Welling and Barbhaiya (1982) found that food increases absorption of chlorothiazide in 9 volunteers while Peloquin e*t al* (1998) found that food increases absorption of pyrazinamide in 16 volunteers. All studies mentioned above explain that food increases absorption of drugs due to improving dissolution of the drugs by delay gastric emptying with increase in drugs residence time in stomach.

The main hypothesis for food impact was the reduced gastric emptying rate and the enhancement of drug dissolution. Our hypothesis in this study is that the impact of food could also be related to the decrease in simvastatin prodrug hydrolysis in the stomach by increasing the gastric pH then increasing simvastatin bioavailability in blood circulation.

The observation of much higher plasma levels of the simvastatin after ingestion with food suggests an additional mechanism of the influence of food on the bioavailability of simvastatin. It remains to explain whether our finding is due to the pH change of gastrointestinal tract, by food, which will increase the stability of lactone form of simvastatin and improve dissolution of the drug by increasing gastric residence time.

Food is able to modify the pH of urine and alter the elimination of certain drugs [32]. As a result of increasing gastric transit time and

gastric acid exposure in the stomach, food can reduce the bioavailability of some acid-labile compounds [32].

The instability of simvastatin at low gastric pH and the different bioavailability of the simvastatin after administration with food indicated that food might modify the bioavailability of the simvastatin. Our results differ from those already collected regarding other acidic labile compounds (e.g. erythromycin) which showed decrease in bioavailability when administered with food [33]. One possible explanation of this discrepancy could be that in case of erythromycin the instability is observed under pH 5 [32]. In fasting state the mean gastric pH is between 1.1 and 1.5 [34]. Briefly after consumption of food the gastric pH is elevated up to 6.7, then decline back to the value of the fasting condition over a period less than 2-3 hr [35]. As food increases the gastric transit time [9] erythromycin molecules remain for more prolonged time in a pH less than 5 which might cause increased degradation.

The critical pH for the instability of simvastatin *in vitro* study by Kaufman (1990) was about 2; therefore the postprandial elevation of the gastric pH prevents the degradation of simvastatin for longer time period. In addition, our results indicate that not all acid-labile compounds behave similarly when they are given with food. The effect of food on the pharmacokinetics of such compounds depends on the value of the critical pH where the acid instability occurs.

In this current study, the absolute bioavailability with food is higher than fasting conditions. There is 50% increase in AUC with food versus fasting conditions. Also, the C_{max} (after a 40 mg simvastatin tablet) is greater with food than while fasting and the T_{max} is also longer. The results in current study display similar pharmacokinetic profile in the presence of food as conducted by previous studies Sommers *et al* (1984); Hughes *et al* (1989); Manciet *et al* (1997). In all these studies drugs are prodrug esters display similar pharmacokinetic profile in the presence of food, which could inhibit cholinesterases activity by food, low gastric pH and have a protecting effect on drugs hydrolysis in the intestinal lumen. The ester becomes partially hydrolyzed by esterases enzymes prior to absorption when the gastric acidity is buffered by food. All studies above concluded that the impact of food could be related to the decrease in prodrug ester hydrolysis in the intestinal lumen by decreasing the rate of release of metabolites free acid which cannot be absorbed by the intestinal wall then excreted in faeces. In addition, the absorption of these compounds was enhanced by food. These may be of delayed gastric emptying and gastrointestinal transit which allow more complete dissolution or prolonged residence at the most favourable site of absorption in the intestine.

The stability of drugs in physiological fluids depends on two factors: the chemical stability of the drug across the gastrointestinal pH range, i.e. the drug's pH stability profile between pH 1 and pH 8, and its susceptibility to enzymatic breakdown by the gastrointestinal fluids [36-37]. Poor bioavailability results if degradation is extensive.

In our study, the observation of much higher plasma levels of the simvastatin after ingestion with food was found. This effect may be due to food increase of the pH of gastrointestinal tract which leads to increasing the stability of lactone form of the simvastatin in GIT and improve dissolution of the drug by increasing gastric residence time.

To the best of the researcher's knowledge, there is no study available to investigate the mechanism of simvastatin absorption with food in healthy younger volunteers. One study has been conducted by [38]. This study is not significant enough to confirm the pharmacokinetic of simvastatin in fasting and non-fasting. In addition, the study was done in elderly patients (mean age 62) with coronary heart disease, while the results showed higher effect in simvastatin tablet taken after food 4 hours than in fasting condition. Others studies have been published shown the drugs interactions with simvastatin [39-40], bioequivalence [41], grapefruit juice interaction with simvastatin [42-43] and pharmacokinetic of simvastatin [5-6].

Based on the results of a previous study conducted by Manciet *et al* (1997); Sommers *et al* (1984); Hughes *et al* (1989), food could inhibit cholinesterases activity by low gastric pH and have a protecting effect on drugs hydrolysis in the intestinal lumen. In this current study simvastatin is prodrug lactone form and the result in this study with food was consistent to the above prodrug esters. Moreover, our results can explain only *in vivo* the impact of food on protecting effect on lactone form of the simvastatin in the gastrointestinal tract. These results could be very useful in protecting this simvastatin prodrug from hydrolysis by gastric acid secretion. This study revealed that simvastatin is pH-dependent.

Finally, no evidence shows failure of simvastatin and absorption in the presence of food. Although giving simvastatin with food led to increased systemic exposure, the incidence of simvastatin was lower when simvastatin was taken with food. Based on this pharmacokinetic analysis, simvastatin may need to be administered in a consistent manner, either always with or always without food. Further clinical studies of the effects of food on simvastatin are warranted.

The *in vivo* study has the usual limitations of a pharmacokinetic study, which may be important in the case of simvastatin. The study was performed in young men (age 31 ± 9.3 years), not in patients who often receive other medications that may have different influences on absorption of simvastatin under fasting and fed conditions. Furthermore, plasma simvastatin levels after a single-dose administration under fasting, fed conditions were used, which may not be readily predictive of the magnitude of corresponding change in electro-physiologic effects of the drug in clinical situations. This current study is recommended further clinical studies of the effects of food on simvastatin in patients who often receive other medications and elderly age should be explored.

CONCLUSION

The concomitant intake of simvastatin with food resulted in considerable and significant higher AUC_{0-24} and C_{max} values for simvastatin, as compared with the ingestion of the simvastatin on an empty stomach. The mean observed T_{max} for simvastatin with food is significant and higher than when intake simvastatin on an empty stomach.

REFERENCES

1 Gruber, P., Rubinstein, A., Li, V.H.K., Bass. P., Robinson, R.J.. Gastric emptying of non-digestible solids in the fasted dog. J. Pharm. Sci. (1987; 76: 117-122.

2 Cortot. A., Colombel. F.J. . Gastric emptying of OROS Tablets in man. Inter. J. Pharm. 1984; 22: 321-325.

3 Carlson, M.G., Ruddon, W.R., Hug, C.C., Bass, P.. Effect of nicotine on Gastric antral and duodenal contractile activity in the dog. *J.* Pharmacol. Exp. Ther 1970; 172: 367-376.

4 Fell, T.J., Digenis, A.G. Imaging and behavior of solid oral dosage forms in vivo. Inter. J. Pharm. 1984; 22**:** 1-15.

5 Mauro, V.F. Clinical Pharmacokinetics and Practical Applications of Simvastatin. J. Clin. Pharmacokinet. 1993; 24: 195-202.

6 Plosker, L.G., Mctavish, D. (). Simvastatin. A reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolanemia. Drugs. 1995; 50: 334-363.

7 Serajuddin, A.T.M., Ranadive, A.S., Mahoney, M.E. Relative lipophilicities, solubilities, and structure pharmacological considerations of 3-HMG-CoA reductase inhibitors pravastatin, lovastatin, mevastatin and simvastatin. J. Pharm. 1991; Sci. 80: 830-834.

8 Kaufman, M.J. Rate and equilibrium constants for acid-catalyzed lactone hydrolysis of HMG-CoA reductase inhibitors. Inter. J. Pharm. 1990; 66: 97-106.

9 Welling, P.G. Effects of food on drug absorption. J. Pharmacol. Ther. 1989; 43: 425-441.

10 Singh, N.B. . Effects of food on clinical pharmacokinetics. J. Clin. Pharmacokinet. 1999; 37: 213-255.

11 u, X.L., Straughn, B.A., Faustino, J.P., Yang, Y., Parekh, A., Ciavarella, B.A., Adjaye, A.E., Mehta, U.M., Conner, P.D., Lesko, J.L., Hussain, S.A. . The Effect of Food on the Relative Bioavailability of Rapidly Dissolving Immediate-Release Solid Oral Products Containing Highly Soluble Drugs. J. Mol. Pharm. 2004; 1: 357-362.

12 Fleisher, D. Li, C., Zhou, Y., Pao, L., Karim, A. Drug, meal and formulation interactions influencing drug absorption after oral administration. J. Clin. Pharmacokinet. 1999; 36:, 233-254.
13 Mithani, S.D., Bakatselou, V., Tenhoor, C.N., Dressman, J.B. (1996). Estimation of the increase in solubility of drug as a function of bile salt concentration. J. Pharm. Res. 1996; 13: 163-167.
14 Dressman, B.J., Amidon, L.G., Reppas, C., Shah, P.V. (1998). Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. J. Pharm. Res. 1998; 15: 11-21.
15 Serajuddin, A.T.M., Rosoff, M., Goldberg, A.H. In situ intestinal absorption of a poorly water soluble drug from mixed micellar solutions of bile salt and lipolysis products in rates. J. Pharm. Res. 1985; 2: 221-224.
16 Melander, A., Danieison, K., Schersten, B., Thulin, T., Wanlin, E. Enhancement by food of canrenone bioavailability from spironolactone. J. Pharmacol. Ther. 1977; 22: 100-103.
17 Overdiek, W.P.M.H., Merkus, W.H.M.F. Influence of food on the bioavailability of spironolactone. J. Clin. Pharmacol. Ther. 1986; 40: 531-536.
18 Melander, A., Danieison, K., Schersten, B., Wahlin,E. Enhancement of the bioavailability of propranolol and metoprolol by food. J. Clin. Pharmacol. Ther. 1977; 22: 108-112.
19 Colburn, A.W., Gibson, M.D., Wiens, E.R., Hanigan, J.J. Food increases the bioavailability of isotretinoin. J. Clin. Pharmacol. 1983; 23: 534-539.
20 Meng, X., Verian, P., Doedee, M., Lin, E., Weinry, I., Chiang, T.S., Kowey, R.P. Bioavailability of AmiodaroneTablets Administered With and Without Food in Healthy Subjects. Am. J. Cardiol. 2001; 87: 432-435.
21 McNamera, P.J., Jewell, R.C., Jenson, B.K., Brindley, C.J. Food increases the bioavailability of acitretin. J. Clin. Pharmacol.1988; 28: 1051-1055.
22 Melander, A., Lalka, D., Mclean, A. Influence of food on the presystemic metabolism of drugs. J. Pharmacol. Ther.1988; 38: 253-267.
23 Wilkinson, R.G. The effects of diet, aging and disease-states on presystemic elimination and oral drug bioavailability in humans. J. Advanced Drug Delivery Reviews. 1997; 27: 129-159.
24 Christians, U., Jacobsen, W., Floren, L. C. Metabolism and Drug Interactions of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Transplant Patients: Are the Statins Mechanistically Similar?. J. Pharmacol. Ther. 1998; 80: 1-34.
25 Fabre, F.L., Timmer, J.C. Effects of Food on the Bioavailability of Gepirone from Extended-Release Tablets in Humans: Results of Two Open-Label Crossover Studies. J. Curr. Ther. Res. 2003; 64: 580-599.
26 Svensson, K.C., Edwards, J.D., Mauriello, M.P., Barde, H.S., Foster, C.A., Lanc, R. A., Jr, M.E., Lalka, D. Effect of food on hepatic blood flow: Implications in the "food effect" phenomenon. J. Clin. Pharmacol. Ther. 1983; 34: 316-323.
27 Svensson, K.C., Edwards, J.D., Mauriello, M.P., Barde, H.S., Jr, M.E., Lalka, D. Effect of carbohydrates on estimated hepatic blood flow. J. Clin. Pharmacol. Ther. 1984; 35: 660-665.
28 Welling, G.P., Lyons, L.L., Tse, S.L.F., Carig, A.W. Propoxyphene and norpropoxyphene: influence of diet and fluid on plasma levels. J. Clin. Pharmacol. Ther.1976; 19: 559-565.
29 Beermann, B., Grind, G.M. Gastrointestinal absorption of hydrochlorothiazide enhanced by concomitant intake of food. Eur. J. Clin. Pharmacol. 1978; 13: 125-128.
30 Welling, G.P., Barbhaiya, H.R. Influence of food and fluid volume on chlorothiazide bioavailability: comparison of plasma and urinary excretion methods. J. Pharm. Sci. 1983; 71: 32-35.
31 Peloquin, A.C., Bulpitt, E.A., Jaresko, S.G., Jelliffe, W.R., James, T.G., Nix, E.D. Pharmacokinetics of pyrazinamide under fasting conditions, with food and with antacid. J. Pharmacol. Ther. 1998; 18: 1205-1211.
32 Drabant, S., Nemes, B.K., Horvath, V., Tolokan, A., Grezal, G., Anttila, M., Gachalyi, B., Kanerva, H., AL-Behaisi, S., Harvai, G., Klebovich, I. Influence of food on the oral bioavailability of deramciclane from film-coated tablet in healthy male volunteers. Eur. J. Pharm. Bioph.2004; 58: 689-695.
33 Rutland, J., Berend, N., Marlin, E.G. The influence of food on the bioavailability of new formulations of erythromycin stearate and base; Br. J. Clin. Pharmacol. 1979; 8: 343-347.
34 Lui, C.Y., Amidon, G.L., Berardi, R.R., Fleisher, D., Youngberg, C., Dressman, J.B. Comparison of gastrointestinal pH in dog and humans: implications on the use of the beagle dog as a model for oral absorption in humans. J. Pharm. Sci. 1986; 75: 271-274.
35 Dressman, B.J., Berardi, R.R., Dermentzoglou, C.L., Russell, L.T., Schmaltz, P.S., Barnett, L.J., Jarvenpaa, M.K. Upper Gastrointestinal (GI) pH in young, healthy men and women. J. Pharm. Res. 1990; 7: 756-761.
36 Gibaldi, M. *Biopharmaceutical and Clinical Pharmacokinetics*, 4th ed. Lea and Febiger, Philadelphia, 1991; U.S.A.
37 Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R. A theorical basis for a biopharmaceutic drug classification: The correlation of in vitro product dissolution and in vivo bioavailability. J. Pharm. Res. 1995; 12: 413-419.
38 Schaefer, E.J., McNamara, J.R., Tayler, T., Daly, J.A., Gleason, J.L., Seman, L.J., Ferrari, A., Rubenstein, J.J. Comparisons effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin) on fasting and postprandial lipoproteins in patients with coronary hear disease versus control subjects. Am. J. Cardiol. 2004; 93: 31-39.
39 Gruer, P.J.K., Vega, J.M., Mercuri. M.F., Dobrinska, M. R., Tobert, J.A. Concomitant use of cytochrome P450 3A4 inhibitors and simvastatin. Am. J. Cardiol.1999; 84, 811-815.
40 Jacobson, T.A. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin and atorvastatin when coadministered with cytochrome p450 inhibitors. Am. J. Cardiol. 2004; 94: 1140-1146.
41 Najib, N.M., Idkaidek, N., Adel, A., Admour, I., Astigarraga, R.E.B., De-Nucci, G., Alam, M.S., Dham, R., Qumaruzaman. Pharmacokinetics and Bioequivalence Evaluation of two Simvastatin 40 mg tablets (Simvastatin and Zocor) in healthy human volunteers. Biopharm. Drug. Dispos. 2003; 24: 183-189.
42 Lilja, J.J., Kivisto, K.T., Neuvonen, P.J. Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. J. Clin. Pharmacol. Ther. 1998; 64: 477-483.
43 Lilja, J.J., Kivisto, K.T., Neuvonen, P.J. Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. J. Clin. Pharmacol. Ther. 2000; 68: 384-390.