Evaluation of Solubilizers in the Drug Release Testing of Hydrophilic Matrix Extended-Release Tablets of Felodipine

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The drug release of felodipine, a water-insoluble drug, was tested by using sodium lauryl sulphate (SLS), polyoxyethylene 20 sorbitan monooleate (Tween) or cetyltrimethylammonium bromide (CTAB) in the test medium as solubilizers. Three slightly different felodipine extended-release (ER) tablets 10 mg based on the gel matrix principle were evaluated under different solubilizer concentrations, agitation intensities and pH. These tablets were also tested in a bioavailability study together with an oral solution. All three solubilizers substantially enhanced the drug solubility and sink conditions were obtained. The choice of solubilizer affected the drug release rate. This is most probably due to physico-chemical interactions between the gel-forming agent and the solubilizers. All in vitro test conditions provided a good correlation (r^2 = 0.94–0.97) to in vivo dissolution, as determined by moment analysis. However, a much steeper in vitro/in vivo relationship was obtained for SLS compared to Tween and CTAB reflecting an inferior discrimination between the tablets by use of this anionic solubilizer.

KEY WORDS: felodipine ER; hydrophilic matrix tablets; solubilizers; in vitro drug release; in vitro/in vivo correlation.

INTRODUCTION

In vitro drug release from a dosage form is a valuable tool in the development of new formulations and production control. Felodipine, an antihypertensive and antianginal calcium-antagonist of the dihydropyridine type, is given as a hydrophilic matrix extended release (ER) tablet. Its release profile affects the plasma concentration-time profile and the clinical effect (1,2). It is therefore important that the in vitro dissolution test method discriminates between formulations which have different in vivo performance.

Felodipine is a water insoluble drug. The development of a discriminative in vitro drug release method therefore becomes complicated by the need to get acceptable solubility of the drug in the test medium. Different approaches to this problem have been suggested, and as a method of choice the addition of a solubilizer to the test medium in amounts providing micellar solubilization has been proposed (3). An in vitro release test method was initially developed for felodipine ER tablets using sodium lauryl sulphate (SLS) as a solubilizer. A good discriminatory ability and a close correlation between in vitro and in vivo release was shown for this method (4). However, a modification of the formulation unexpectedly resulted in poor separation in vitro between formulations providing different plasma concentrations.

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The aim of the present study was therefore to evaluate if other solubilizers might improve the predictive value of the in vitro release. Cetyltrimethyl ammonium bromide (CTAB) and polyoxyethylene 20 sorbitan monooleate (Tween) were chosen as representatives for cationic and neutral surfactants, respectively, in contrast to the anionic SLS.

MATERIALS AND METHODS

Materials

SLS (specially pure, BDH, England), Tween (Merck, Germany) and CTAB (Merck, Germany) were used as received. Felodipine, 5-ethyl-3-methyl-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Astra, Sweden) was of 99.6% purity. All other chemicals were of analytical grade.

The study included three felodipine 10 mg ER tablets (A, B and C) of hydrophilic matrix type, i e a gel is formed at the tablet surface in contact with aqueous fluids. Release of nonsoluble drugs from this type of ER tablets occurs by erosion of the gel layer (5). Tablet A, B and C had identical compositions except for the viscosity of the gel-forming agent, hydroxypropyl methylcellulose (HPMC). The tablets were made by conventional wet granulation followed by compression to circular tablets (diameter 9 mm). In the bioavailability study, a hydroalcoholic solution (S) of felodipine 1 mg/ml was included as a reference.

Solubility of felodipine in micellar solutions

Aqueous suspensions of felodipine (2 mg/ml) were equilibrated for 24 hours at 37°C in 50 ml of 0.1 M phosphate buffer pH 6.5 in the presence of one of the three different solubilizers at three different concentrations well above the critical micelle concentration (CMC). The equilibrium solubility was measured spectrometrically at 362 nm.

In vitro drug release

An USP dissolution apparatus No 2 (paddle) modified with a stationary basket was used (4). The individual tablets were placed into the baskets to obtain reproducible hydrodynamic test conditions. The experimental conditions were varied according to table I. In all experiments six individual tablets were tested. The test medium contained either 500 ml 0.1 M phosphate buffer (pH 6.5) or 0.1 M HCl (pH 1.2) thermostated to 37°C. The amount of felodipine released was measured spectrometrically at 362 nm.

The drug release was quantified by the mean dissolution time (MDTvitro) (6). MDTvitro was defined as the time when 50% of the drug had been released, determined by linear regression, since the in vitro dissolution could be approximated to zero order kinetics.

Tablet erosion

The in vitro tablet erosion was determined using the same equipment as for the in vitro drug release experiments. The tablets were removed from the dissolution apparatus at different times and weighed after drying to constant weight.

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Table I. Mean (SD) MDTvitro for All in vitro Dissolution Experiments (n = 6)

No	Solubilizer concentration (w/v %)	pH	Stirring rate (rpm)	MDTvitro (h) tablet A	B	C
1	0.5% SLS	6.5	100	—	3.3 (0.1)	—
2	1.0% SLS	6.5	100	2.2 (0.1)	2.7 (0.1)	3.2 (0.1)
3	1.0% SLS	1.2	100	—	3.1 (0.1)	—
4	1.0% SLS	6.5	50	3.8 (0.1)	5.2 (0.2)	6.6 (0.1)
5	1.5% SLS	6.5	100	—	2.4 (0.1)	—
6	1.0% Tween	6.5	100	—	3.3 (0.1)	—
7	2.0% Tween	6.5	100	2.1 (0.1)	3.5 (0.1)	6.0 (0.2)
8	2.0% Tween	1.2	100	—	4.1 (0.1)	—
9	2.0% Tween	6.5	50	3.4 (0.1)	5.8 (0.1)	10.5 (0.3)
10	3.0% Tween	6.5	100	—	3.6 (0.1)	—
11	0.2% CTAB	6.5	100	—	3.2 (0.1)	—
12	0.4% CTAB	6.5	100	1.9 (0.1)	3.4 (0.1)	5.3 (0.2)
13	0.4% CTAB	1.2	100	—	3.5 (0.1)	—
14	0.4% CTAB	6.5	50	2.9 (0.1)	5.7 (0.2)	8.1 (0.3)
15	0.6% CTAB	6.5	100	—	3.1 (0.1)	—

—, not determined.

Tablet erosion was expressed as percentage of the initial weight. Experiments investigating erosion with 1.0% SLS, 2.0% Tween, 0.4% CTAB and without solubilizer were performed for tablet C at a paddle stirring rate of 100 rpm in phosphate buffer pH 6.5 as duplicate measurements. The mean erosion time (MET) was calculated by using the same procedure as for the assessment of MDTvitro.

Bioavailability study

The study was of an open, four-way, randomised, cross-over design including tablets A, B, C and the oral solution in 16 young, healthy, male subjects. All subjects received each of the four formulations. The treatments were given as a single dose of 10 mg felodipine in the morning after an overnight fast. The study was performed according to the declaration of Helsinki and was approved by the local ethics committee. The concentration of felodipine in plasma was determined by gas chromatography with electron capture detection (7). The minimum determinable concentration (RSD < 15%) was 1 nmol/L.

The in vivo dissolution-time curves for the three felodipine ER tablets were determined by numerical deconvolution of individual data using the plasma concentration data from the oral solution as the weighting function (8). The mean dissolution time in vivo (MDTvivo) was determined by applying moment analysis on the in vivo dissolution-time data (9). The area under the plasma concentration-time profile (AUC) from 0 h to infinity and the relative bioavailability (Frel) for the three ER tablets in relation to the oral solution was calculated. The difference in MDTvivo and AUC between the study drugs was analysed using pairwise t-tests based on an ANOVA.

RESULTS

Solubility of felodipine

The results are presented in table II. The solubility of felodipine was increased substantially by adding a solubilizer in concentrations well above CMC compared to the solubility of the drug in pure water. The solubilization capacity differed somewhat between the solubilizers which reflected the difference in CMC. The drug solubility was of the same magnitude in 1.0% SLS, 2.0% Tween and 0.4% CTAB.

In vitro drug release

The in vitro release rate differed between the three felodipine ER tablets A, B and C irrespective of the testing conditions as shown by the MDTvitro values given in table I. Tablet A had the fastest drug release, B was intermediate and C was the slowest in all experiments. All three tablets had an almost linear release profile up to about 90% dissolved. The linearity of the dissolution-time profile between 0–90% dissolved was verified by the coefficient of determination (r^2) obtained in the linear regression of the dissolution time data which was ≥0.99 in all cases. The variability between the individual tablets (n = 6) in the determinations of amount dissolved at each test time was low as shown by the standard deviations (SD) depicted in figure 1a–c.

The in vitro release rate for each tablet differed some-

Table II. Solubility of Felodipine at 37°C in Phosphate Buffer pH 6.5 Containing Different Amounts of SLS, Tween or CTAB

Solubilizer	Solubilizer concentration (w/v %)	Solubility of felodipine (mg/l)
—	0	1
SLS	0.5	340
	1.0	720
	1.5	1110
Tween	1.0	480
	2.0	990
	3.0	1230
CTAB	0.2	490
	0.4	970
	0.6	1480

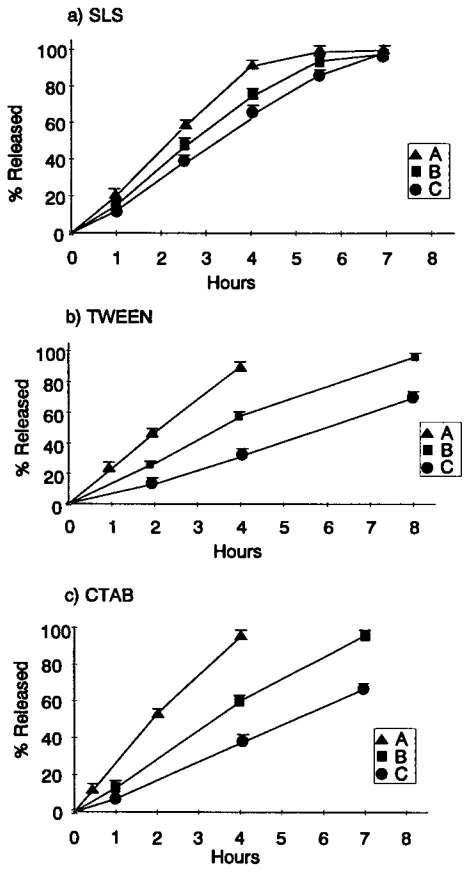

Figure 1a–c Mean (SD) cumulative in vitro release-time profiles of felodipine for tablet A, B and C in buffer pH 6.5 containing a) 1.0% SLS b) 2.0% Tween c) 0.4% CTAB at a paddle stirring rate of 100 rpm (n = 6)

what between the different types of solubilizers. This resulted in varying degrees of discrimination between the tablets as shown in figures 1a–c. The release rate for the three different formulations was quite similar in the presence of SLS (experiment No 2) as shown by MDTvitro for A, B and C being 2.2, 2.7 and 3.2 h, respectively. When using Tween or CTAB a more pronounced difference in the dissolution rate was observed between the different tablets. For Tween and CTAB (experiment Nos. 7 and 12) the MDTvitro for tablets A, B and C was 2.1, 3.5, 6.0 h and 1.9, 3.4, 5.3 h, respectively. The same pattern was found regarding the comparison between the different solubilizers irrespective of the paddle stirring rate. The release rate was however slower for all tablets at the lower stirring rate (experiment Nos. 4, 9 and 14) as reflected by the about twice as high MDTvitro values.

Tablet B was tested at different concentrations of the three solubilizers. The release rate, reflected by MDTvitro, was very little affected by the use of different concentrations of Tween and CTAB, while it was increased by higher concentration of SLS.

The release rate in 0.1 M HCl was almost the same as in phosphate buffer pH 6.5 irrespective of the surfactant (see table 1).

Tablet erosion

The erosion of tablet C, which was most affected by the choice of solubilizer in the dissolution testing, is depicted in figure 2. The variability in the determination of tablet erosion was low as indicated by the maximum range of 3% between the individual tablets for any measurement. The erosion proceeded at an approximately constant rate in all four experiments. The erosion rate differed between the solubilizers with the mean erosion time (MET) being 3.1 h, 5.7 h and 4.4 h for SLS, Tween and CTAB, respectively. The MET obtained without solubilizer was 4.8 h. Tablet erosion in the presence of SLS was clearly faster than in plain buffer whereas the use of Tween and CTAB was more similar to plain buffer.

In vivo study

The mean plasma concentration-time profiles following the three different ER tablets and the oral solution are shown in figure 3. The mean (SD) cumulative in vivo dissolution time profiles for the three ER tablets are shown in figure 4. The mean (SD) bioavailability variables derived are summarised in table III.

All three tablets possessed ER properties when compared with the oral solution. The different in vitro release rates for the tablets were reflected in vivo by well separated in vivo dissolution and plasma concentration profiles. The in vivo dissolution rates were significantly different with the MDTvivo being 3.3, 7.6 and 11.5 h for tablet A, B and C, respectively. The extent of absorption, as reflected by AUC, was not significantly different between the tablets. The mean bioavailability in relation to the solution (S) was 88%, 95% and 87% for tablets A, B and C respectively.

In vitro/in vivo correlation

The relation between individual MDTvivo values and the corresponding MDTvitro data was evaluated by using linear regression analysis. The mean linear in vitro/in vivo relationships for all data together with the coefficient of determination (r^2) are given in table IV. The average linear relationships obtained for the three solubilizers for the in vitro dissolution test performed at a paddle stirring rate of 100 rpm are depicted in figure 5. MDTvitro data obtained for the three different solubilizers all correlated well to MDTvivo as indicated by the high r^2 values (0.94–0.97). However, the relationship between the in vitro and in vivo drug release differed between the three solubilizers. The

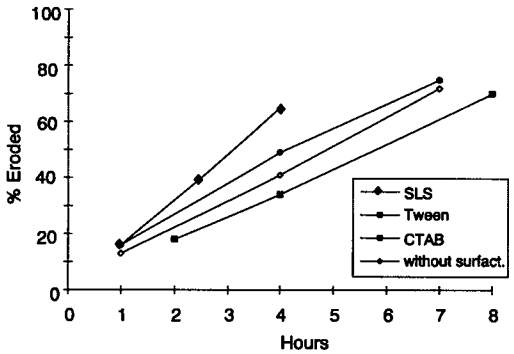

Figure 2 Mean erosion of tablet C in plain buffer pH 6.5 with 1.0% SLS, 2.0% Tween, 0.4% CTAB or without surfactant (n = 2)

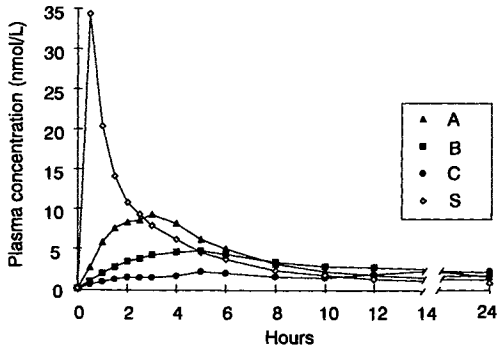

Figure 3 Mean felodipine plasma concentration for tablet A, B, C and the oral solution (S) (n = 16)

steepest in vitro/in vivo relationship was obtained for SLS, i.e. the in vitro dissolution test provided the smallest differences between tablets which were clearly different in vivo. The lower discriminatory ability for SLS was most pronounced at the higher paddle stirring rate, but this difference between SLS and the other two solubilizers was also apparent at less vigorous agitation. Another different characteristic for SLS compared to the other surfactants was the clear deviation from zero to the intercept obtained in the linear regressions.

DISCUSSION

The in vitro release rate of felodipine from hydrophilic matrix tablets was influenced by the choice of solubilizer. The differences in release rates found for the three solubilizers could not be explained by different solubilization capabilities since the drug solubility was roughly the same for 1.0% SLS, 2.0% Tween and 0.4% CTAB. Moreover, the drug solubility was also well above the requirements for attainment of sink conditions (10) in all experiments. A more probable reason is an interaction between the solubilizer and HPMC, the release rate determining excipient of the tablets. It has previously been shown that after addition of solubilizers to a HPMC solution aggregates are formed between the polymer and the solubilizers and the cloud point is lowered (11). These physico-chemical interactions were more pronounced for SLS than for CTAB, and they were judged to be significant for drug release from a HPMC matrix. The release of a water-insoluble drug from a HPMC gel matrix proceeds by erosion at the surface of the gel (5). This was

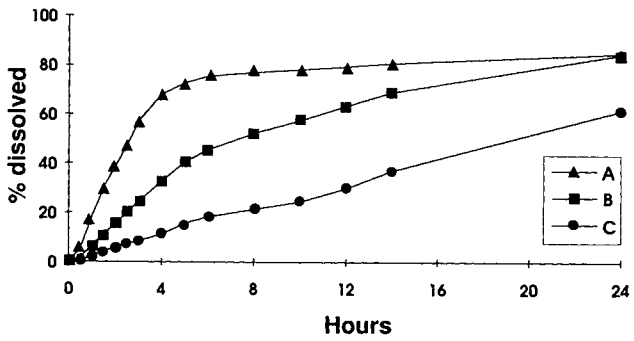

Figure 4 Mean (SD) cumulative in vivo dissolution of felodipine for tablet A, B and C (n = 16)

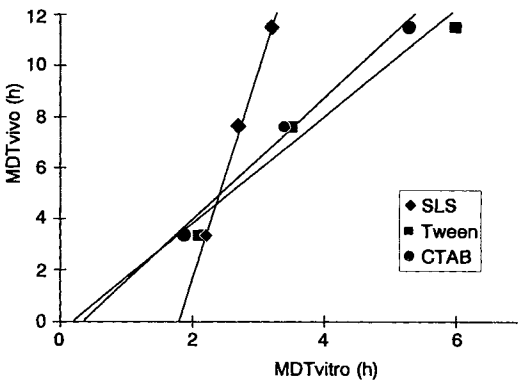

Figure 5 MDTvivo as a function of MDTvitro for 1.0% SLS, 2.0% Tween or 0.4% CTAB in buffer pH 6.5 at a paddle stirring rate of 100 rpm

also confirmed in the present study by the similarity between drug release and tablet erosion rate for tablet C. In order to verify that the differences in release rate demonstrated in the present study was related to solubilizer effects on the release mechanism, the tablet erosion was measured for tablet C in the presence of the different solubilizers and in plain buffer. The different erosion rates obtained indicated that the solubilizers exerted a varying grade of influence upon the function of the gel matrix. The most notable effect was obtained for SLS which had the largest difference of tablet erosion rate compared to plain buffer. Other data further supporting a more pronounced interaction for SLS was the change of in vitro drug release seen with increasing concentrations of SLS whereas the release rate was essentially independent of surfactant concentration for the other two.

Interactions between components in the in release test media and the dosage forms could obscure the interpretation of the in vitro results unless the interactions are physiologically relevant. Corresponding effects to those described above could potentially be exerted in vivo by the bile salts which are solubilizing agents. However, in the present case the use of SLS but not CTAB and Tween substantially diminished the difference in in vitro release rate between the three tablets which were clearly different in vivo. Thus, the influence of SLS on the tablet matrix in vitro seemed not to reflect any physiological effect. This is also in accordance with results from physico-chemical experiments showing almost no interaction between bile salts (sodium cholate and sodium taurocholate) and HPMC (11).

It is highly desirable to develop an in vitro release method that correlates to in vivo data. This aim was fulfilled for felodipine ER tablets by use of Tween, CTAB and also for

Table III. Mean (SD) Bioavailability Variables after Single Dose Administration of Felodipine 10 mg (n = 16)

Formulation	MDTvivo (h)	AUC (nmol · h/L)	Frel (%)
A	3.3 (1.5)	88 (37)	88 (14)
B	7.6 (1.6)	92 (32)	95 (17)
C	11.5 (1.2)	86 (41)	87 (29)
S	0	99 (34)	100

Table IV. Linear Regression Analysis of the Relationship Between MDTvivo (y) and MDTvitro (x) Under Different in vitro Dissolution Conditions for Tablet A, B and C

Experimental conditions	Relationship	r^2
1.0% SLS, 100 rpm, pH 6.5	$y = 8.1x - 14.8$	0.97
2.0% Tween, 100 rpm, pH 6.5	$y = 2.1x - 0.5$	0.94
0.4% CTAB, 100 rpm, pH 6.5	$y = 2.4x - 0.9$	0.96
1.0% SLS, 50 rpm, pH 6.5	$y = 2.9x - 7.4$	0.97
2.0% Tween, 50 rpm, pH 6.5	$y = 1.1x + 0.1$	0.94
0.4% CTAB, 50 rpm, pH 6.5	$y = 1.6x - 1.2$	0.97

SLS despite the suggested non-physiologic interaction with HPMC. However, SLS seems to be less appropriate when utilizing the in vitro/in vivo relationship in the development of new tablets of the present type. For example, the intercept of the relationship between MDTvitro and MDTvivo deviated considerably from the origin for SLS. This implied an initial non-linear part of the in vitro/in vivo relationship. Predictions of in vivo dissolution for tablets having a faster release rate than A is thus of very limited value. Another unfavourable implication of the high intercept for SLS is that the ratio between in vitro and in vivo dissolution becomes strongly dependent on the release rate also within the range covered by tablet A, B and C. This means that a simple time scaling factor cannot be used to predict in vivo dissolution from in vitro data. In addition, the slope of the in vitro/in vivo relationship was very steep for SLS compared to Tween and CTAB, especially at the higher paddle stirring rate. Consequently, a small change in in vitro release corresponds to a relatively large change in the plasma concentration profile. In vivo predictions under such circumstances will be susceptible to uncontrolled variability of the in vitro release data. Regarding the use of the release test method as a batch control in regular production, all three solubilizers could be used based on the solubilizers equally good correlations although SLS is less favourable due to other reasons discussed above.

In conclusion, a discriminative in vitro drug release test with very good correlation to in vivo data was obtained for felodipine ER tablets by including SLS, Tween or CTAB as solubilizer in the test media. However, SLS was less suitable since it provided inferior discrimination between the different tablets and a more complicated in vitro/in vivo relationship most probably as a result of physico-chemical interactions with HPMC, the release rate controlling ingredient. This study thus confirmed that addition of a solubilizer is a feasible way to obtain sink conditions for the in vitro release testing of ER formulations containing water insoluble drugs. However, the choice of solubilizer must be carefully evaluated due to the possibility of interactions between the solubilizer and the release rate controlling excipients of the dosage form.

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REFERENCES

1. E Blychert, K Wingstrand, B Edgar and K Lidman. Plasma concentration profiles and antihypertensive effect of conventional and extended-release felodipine tablets. Br J Clin Pharmac 29:39–45 (1990).
2. PHJM Dunselman, B Edgar. Felodipine clinical pharmacokinetics. Drugs 21:418–430 (1991).
3. V P Shah, J J Konecny, R L Everett, B McCullough, A C Noorizaden, J P Skelly. In vitro dissolution profile of water-insoluble drug dosage forms in the presence of solubilizers. Pharm Res 6:162–618 (1989).
4. K Wingstrand, B Abrahamsson, B Edgar. Bioavailability from felodipine extended-release tablets with different dissolution properties. Int J Pharm 60:151–156 (1990).
5. D A Alderman. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int J Pharm Tech & Prod Mtr 5:1–9 (1984).
6. S Riegelman, P Collier. The application of statistical moment theory to the evaluation of the in vivo dissolution time and absorption time. J Pharmacokinet Biopharm 8:509–534 (1980).
7. M Ahnoff. Determination of felodipine in plasma by capillary gas chromatography with electron capture detection. J Pharm Biomed Anal 2:519–26 (1984).
8. F Langenbucher. Numerical convolution/deconvolution as a tool for correlating *in vitro in vivo* drug availability. Pharm Ind 44:1166–1172 (1982).
9. H M v Hattingberg. Moment analysis in vitro and in vivo. Meth and Find Exptl Clin Pharmacol 6:589–595 (1984).
10. M Gibaldi, S Feldman. Establishment of sink conditions in dissolution rate determinations. J Pharm Sci 56:1238–1242 (1967).
11. J E Löfroth, L Johansson, A C Norman, K Wettström. Interactions between solubilizers and polymers I: HPMC Progr Colloid Polym Sci 84:1–5 (1991).