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Research Article

Improved Oral Bioavalability of Mebudipine Upon Administration in PhytoSolve and Phosal-Based Formulation (PBF)

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Abstract. The aim of this investigation was to examine the efficacy of PhytoSolve and Phosal-based formulation (PBF) to enhance the oral bioavailability of mebudipine, which is a poorly water-soluble calcium channel blocker. The solubility of mebudipine in various oils was determined. PhytoSolve was prepared with a medium-chain triglyceride (MCT) oil (20%), soybean phospholipids (5%), and a 70% fructose solution (75%). The influence of the weight ratio of Phosal 50PG to glycerol in PBF on the mean globule size was studied with dynamic light scattering. The optimized formulation was evaluated for robustness toward dilution, transparency, droplet size, and zeta potential. The *in vivo* oral absorption of different mebudipine formulations (PhytoSolve, PBF, oily solution, and suspension) were evaluated in rats. The optimized PBF contained Phosal 50PG/glycerol in a 6:4 ratio (*w*/*w*). The PBF and PhytoSolve formulations were miscible with water in any ratio and did not demonstrate any phase separation or drug precipitation over 1 month of storage. The mean particle size of PhytoSolve and PBF were 138.5±9.0 and 74.4±2.5 nm, respectively. The *in vivo* study demonstrated that the oral bioavailability of PhytoSolve and PBF in rats was significantly higher than that of the other formulations. The PhytoSolve and PBF formulations of mebudipine are found to be more bioavailable compared with suspension and oily solutions during an *in vivo* study in rats. These formulations might be new alternative carriers that increase the oral bioavailability of poorly water-soluble molecules, such as mebudipine.

KEY WORDS: mebudipine; oral bioavailability; Phosal 50PG; PhytoSolve.

INTRODUCTION

Mebudipine [(±)-*t*-butyl,methyl-1,4-dihydro-2,6-dimethy-4-(3-nitrophenyl)-3,5-pyridine dicarboxylate] was first synthesized in 1997 by Mahmoudian *et al.* as a new 1,4-dihydropyridine derivative and calcium channel antagonist (1). Mebudipine acts as an L-type voltage-dependent calcium channel blocker and has pharmacological effects similar to those of nifedipine (2). Previous studies have demonstrated that mebudipine exhibited some advantages over nifedipine, such as better vasoselectivity (3) and desirable pharmacokinetic properties, including a longer biological half-life and a slower onset of maximum effect (4).

However, animal models have shown that mebudipine's oral bioavailability is very low (4), which is similar to the oral bioavailability of similar compounds, such as nimodipine (5), nitrendipine (6), nicardipine (7), and nifedipine (8). Slow rates of dissolution and extensive first-pass effects cause the low oral bioavailability of these dihydropyridines. Generally, low oral bioavailability causes intersubject variability and poor therapeutic effects; therefore, developing new formulations to improve the solubility and bioavailability of active compounds is a challenging task.

PhytoSolve formulations are some of the most recent, promising, and novel approaches used to increase the solubility of lipophilic substances. This technique uses only natural ingredients without any preservatives or synthetic surfactants; therefore, a lipophilic active molecule might be dissolved with a matrix of phospholipid/water/polyol or carbohydrate. This formulation ultimately achieves a transparent to a translucent water-soluble concentrate with a particle size of approximately 100 nm (9). Wajda *et al.* have reported that PhytoSolve enhances the bioavailability of coenzyme Q10 and vitamin E relative to the pure substances (10). Previous studies have revealed that phospholipids (one of main components of PhytoSolve formulation) can be used to increase the bioavailability, permeability, and release profile of drugs with poor water solubility. In addition, phospholipids protect drugs from degradation in the gastrointestinal tract (11).

Phosal 50PG is another compound used in some lipid-based formulations to improve the absorption, effectiveness, and therapeutic index of the active ingredients (12).

Despite the benefits of oral lipid-based formulations for delivering water-insoluble drugs, such as improving gastrointestinal absorption, reducing the positive food effect, and simplifying the developmental and manufacturing processes, only 2–4% of the commercially available drug products formulated rely on this technology. The lack of sufficient attention to lipid-based formulations prior to clinical testing on

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insoluble molecules, especially those with anticipated low or variable oral bioavailability in conventional formulations, has led to a dearth of applications for this useful technology (13).

This study evaluates the ability of PhytoSolve techniques and Phosal 50PG formulations to improve mebudipine's bioavailability through *in vivo* studies with rats; the results of this study suggest guidelines for appropriate formulation during clinical testing.

MATERIALS AND METHODS

Materials

Mebudipine and dibudipine (internal standard) were purchased from Pars Biopharmacy Research Co. (Tehran, Iran). Phosal 50PG, Phosal 53 medium-chain triglyceride (MCT), soybean lecithin (LIPOID S75), and MCT oil were donated by Lipoid GmbH (Ludwigshafen, Germany). The vegetable oils were provided by Barij Essence co. (Kashan, Iran). Deionized water was obtained from a Milli-Q water purification system (Millipore, USA). All solvents and additives for the HPLC studies were purchased from Merck Co. (Darmstadt, Germany).

Solubility Study

To determine the solubility of mebudipine in various substances, an excess of the drug was added to 1 mL of each vehicle and vortexed vigorously for 10 min. The mixture was shaken with a shaker for 48 h until equilibrium was reached. Subsequently, the suspension was centrifuged (Eppendorf, Germany) at 3,000 rpm for 20 min and the excess-insoluble mebudipine was separated by filtration through a 0.2-μm syringe filter (Whatman, Germany). The mebudipine concentration in various components was measured via high-performance liquid chromatography (HPLC).

Preparation of PhytoSolve

Mebudipine PhytoSolve was prepared according to the PhytoSolve technique described previously by Wajda (9). In summary, 0.5 g LIPOID S 75 was dispersed in 7.5 g of a 70% fructose solution by vigorous vortexing before the mixture was homogenized for 3 min using an Ultra-Turax homogenizer (IKA® T10B, Germany). Subsequently, 20 mg of mebudipine was dissolved in 2 g of MCT oil and added to the above mixture. After vigorous vortexing, the mixture was sonicated with a probe-type sonicator (Hielscher, Germany) with a 70% amplitude and cycle 0.6 for 10 min. Finally, an emulsion-like mixture that was miscible with water in any ratio was obtained. Furthermore, other formulations with various polyol phases, such as Glycerol or a 70% sucrose solution, were prepared according to the above method to evaluate the effect of the polyol phase on the mean globule size of PhytoSolve formulations.

Preparation of PBF

A series of formulations were prepared with different weight ratios of Phosal 50PG to glycerol between 1:9 and 9:1. A consistent amount of mebudipine was dissolved in Phosal 50PG for all formulations before glycerol was added. This mixture was homogenized for 10 min. After the addition of water, the mixture was vortexed and sonicated using a probe sonicator for 10 min. The mixture was stored at room temperature until used. Table I lists the compositions of various PBFs.

Characterization of Formulations (PhytoSolve-PBF)

Robustness to Dilution

Final formulations were diluted 50, 100, 500, and 1,000 times with distilled water to visually assess any phase separation or drug precipitation immediately, as well as after 24 h, 1 week, and 1 month.

Percentage Transmittance

A UV–visible Spectrophotometer (Pharmacia Biotech, England) was used to determine the transparency of the formulations. Percentage transmittance of diluted formulations (200 times) with double distilled water was measured at 650 nm using double distilled water as blank.

Droplet size Analysis

The mean droplet sizes and polydispersity indices of the formulations were measured using dynamic light scattering with a Zetasizer Nano (Malvern, UK) at a 90° angle to measure the Brownian motion; the size of the particles was determined by illuminating the particles with a laser and analyzing the intensity of the fluctuations in the scattered light (14). The formulation (50 μL) was diluted to 5 mL with double-distilled water to avoid particle interactions and additional scattering during measurement. The dispersant viscosity was set at 0.8872 cP at 25°C.

Determination of Zeta Potential

The formulation (50 μL) was diluted 100 times with double distilled water and its zeta potential was measured with a Zetasizer Nano. The Zetasizer Nano series calculates the zeta potential by determining the electrophoretic mobility and subsequently applying the Henry equation.

Transmission Electron Microscopic Analysis

Transmission electron microscopic (TEM) analysis was used to study the morphology and structure of mebudipine-containing PhytoSolve and PBF. Samples (50 μL) of the diluted formulations were added to a 200-mesh film grid and dried at room temperature. The samples were stained with uranyl acetate and observed with a LEO 906 transmission electron microscope (ZEISS, Germany).

Pharmacokinetic Study

Male Wistar rats weighing 250–300 g were purchased from the Razi institute (Karaj, Iran). The animals had free access to food and water. They fasted overnight before each experiment. The animals were randomly divided into four groups of six rats. The rats were maintained under standard

Table I. Composition of Various Phosal-Based Formulations

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Phosal 50PG (mg)	100	200	300	400	500	600	700	800	900
Glycerol (mg)	900	800	700	600	500	400	300	200	100
Mebudipine (mg)	5	5	5	5	5	5	5	5	5
Water(mL)	5	5	5	5	5	5	5	5	5

Formulations (F1–F9) were prepared in different weight ratio of Phosal 50PG to glycerol from 1:9 to 9:1

laboratory conditions. The use and condition of the animals were approved by the Ethics committee of the Tehran University of Medical Sciences. The mebudipine formulations (PhytoSolve, PBF, oily solution, and suspensions) were administered orally to rats with a gavage needle at a constant dose of 10 mg/kg. The oily solution consisted of MCT oil as the solvent and the mebudipine suspension contained a small amount of hydroxymethylcellulose as a suspending agent and water (5). Blood samples (0.5 mL) were collected from the right external jugular vein through a catheter that was implanted 48 h before sampling (15). Blood samples were collected into heparinized tubes and immediately centrifuged at 5,000 rpm for 20 min. The plasma was separated and stored at −20°C until analysis by HPLC.

Determination of Mebudipine Plasma Levels

The plasma concentrations of mebudipine were determined by HPLC. The HPLC system consisted of a 600 pump (Younglin, Korea), a UV–vis detector (Younglin, Korea), a manual injector (Younglin, Korea), software (Autochro-2000) and a tracer excel ODS-A analytical column (4.6×250 mm, 5 μm). The mobile phase was composed of methanol–water–acetonitrile (70–25–5) at a 1-mL/min flow rate during analysis. The wavelength used for detection was 238 nm. All of the HPLC grade solvents were filtered through a membrane filter (0.45 μm) and sonicated for 10 min in bath sonicator (Starsonic 60, Italy) before use. Mebudipine was extracted from the rat plasma via the liquid-liquid extraction method previously reported by Bohlooli *et al.* with slight modifications (16).

Briefly, 10 μL dibudipine (4 μg/mL) was added to the plasma sample as an internal standard. After 10 s of mixing, 200 μL of NaOH (1 N) was added and the sample was vortexed for 1 min. Subsequently, 2 mL of dichloromethane was added and vortexed vigorously for 5 min. The mixture was centrifuged at 5,000 rpm at 20°C for 25 min. The organic layer was transferred to a separate tube and dried under flowing nitrogen in a water bath (40°C). The dried extract was reconstituted in 100 μL of the mobile phase and, after thorough mixing, 20 μL of the sample was injected onto the HPLC column. The accuracy and precision of method, as well as the calculation of intra- and interday analytical variability were determined by analyzing the concentration of 10, 100, 500, and 1,000 ng/mL mebudipine samples in blank plasma (n=5). The calibration curves were prepared with five concentrations (10, 50, 100, 500, and 1,000 ng/mL) of mebudipine and checked for linearity. The recovery percentage of the mebudipine was determined by comparing the peak area of the extracted mebudipine with the peak area obtained by the direct injection of a pure standard mebudipine sample in mobile phase at three different concentrations (100, 500, and 1,000 ng/mL).

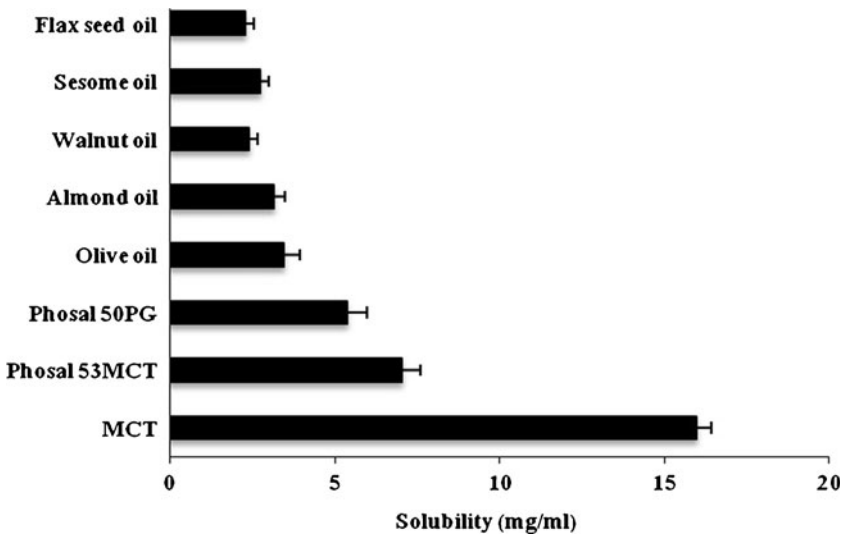

Fig. 1. Solubility of mebudipine in various oils at 25°C; data expressed as the mean±SD

Table II. Composition, Mean Droplet Size, Polydispersity Index, and Zeta Potential of Different PhytoSolve Formulations

	Components of formulation					
Code	Oil	Polyol	Phospholipid	Mean droplet size±SD (nm)	PDI±SD	Mean zeta potential±SD (mv)
PF	MCT	Fructose	Lipoid S75	138.5±9.0	0.12±0.02	−18.43±0.20
PG	MCT	Glycerol	Lipoid S75	145.7±7.2	0.11±0.02	−18.32±0.13
PS	MCT	Sucrose	Lipoid S75	151.7±8.4	0.09±0.04	−18.53±0.40

Data expressed as the mean±SD (n=6)
PDI polydispersity index, *PF* PhytoSolve formulation which contained fructose solution, *PG* PhytoSolve formulation which contained glycerol solution as polyol phase, *PS* PhytoSolve formulation which contained sucrose solution as polyol phase

Pharmacokinetic Data Analysis

The pharmacokinetic parameters, such as the maximum concentration (C_{max}), the time needed to reach the maximum concentration (T_{max}), the area under the plasma drug concentration–time curve from 0 to t h ($AUC_{0\to t}$), the area under the plasma drug concentration–time curve from 0 h to infinity ($AUC_{0\to\infty}$), and the half-life ($T_{1/2}$), were calculated to evaluate the oral bioavailability of the different formulations. C_{max} and T_{max} values were obtained directly from the concentration *versus* time curve. $AUC_{0\to 6\ h}$ was calculated through the linear trapezoidal method. The $AUC_{0\to\infty}$ was calculated via the sum of the areas obtained by the trapezoidal rule ($AUC_{0\to 6\ h}$), and the residual area ($AUC_{6\ h\to\infty}$). The residual area and $T_{1/2}$ were obtained according to following equations (17):

$$AUC_{t\to\infty} = Ct/Ke \quad (1)$$

$$T_{1/2} = \ln\ 2/Ke \quad (2)$$

As the same doses of different formulation were administered orally, the relative bioavailability of each formulation was calculated with respect to the reference (mebudipine suspension) using the following equation:

$$\text{Percent relative bioavailability} = \left(AUC_{0\to\infty}\text{product} \Big/ AUC_{0\to\infty}\text{reference}\right) \times 100 \quad (3)$$

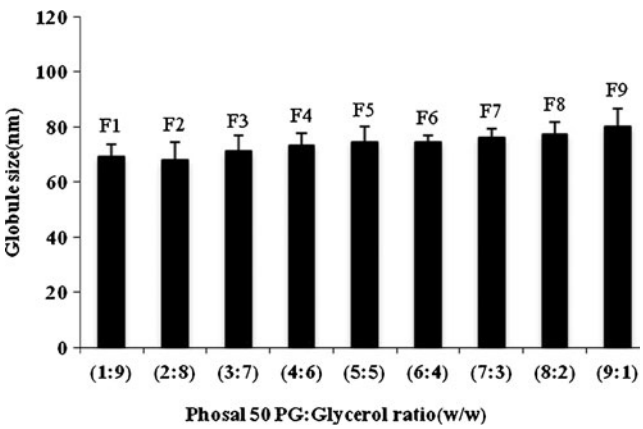

Fig. 2. The effect of Phosal 50PG: glycerol ratio (*w*/*w*) on mean globule size of various mebudipine PBF (*F1* to *F9*). Data were expressed as the mean±SD, (n=3)

Statistical Analysis

The data from the pharmacokinetic and particle size studies were compared for statistical significance via a one-way analysis of variance followed by a Tukey post hoc test at a level of significance of $p<0.05$ using SPSS software (version 14).

RESULTS

Solubility Study

Mebudipine is quite insoluble in water (0.48–0.5 mg/L). Therefore, finding a safe solvent to keep this drug dissolved in formulations is very important. As illustrated in Fig. 1, MCT and Phosal 50PG had superior solubilizing capacity over the other tested lipophilic solvents. Therefore, they were chosen as the oil phase for the development of the formulations. However, the formulations prepared with Phosal 53MCT were unstable; phase separation occurred during storage.

Preparation and Characterization of Formulation

In this study, a PhytoSolve technique was used to enhance solubility of mebudipine in water. Different PhytoSolve formulations using various polyol phases (glycerol, fructose, and sucrose solution) were also prepared. The results have indicated the changes to the composition had a negligible effect on the particle sizes and zeta potentials of these formulations (Table II). PhytoSolve formulations containing fructose had the smaller particle size and was therefore selected for the next experiment.

Additionally, a new formulation using Phosal 50PG, which is an easy-to-use carrier for lipophilic compounds, in addition to glycerol was prepared. The results of the droplet size analysis have revealed that the difference in the weight ratio of Phosal 50PG to glycerol did not affect the mean

Table III. Physicochemical Parameters of the Optimized Mebudipine Formulations

	values	
Parameters	PhytoSolve	PBF
Droplet size(nm)	138.5±9.0	74.4±2.5
Zeta potential (mv)	−18.43±0.20	−2.23±0.15
%Transmittance	78.2±0.2	85.8±0.3

Data were expressed as the mean±SD, n=3

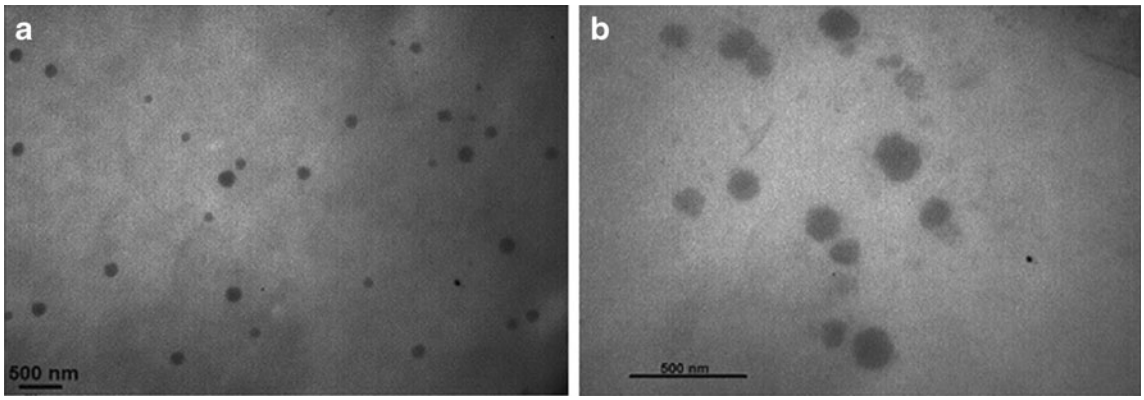

Fig. 3. Transmission electron micrographs of the mebudipine-containing **a** PhytoSolve and **b** Phosal-based formulation. The *scale bar* represents a distance of 500 nm

globule size of the formulations considerably (Fig. 2). Of these ratios (*w*/*w*), F6 (Phosal/glycerol=6:4) was selected for the bioavailability studies.

In addition to the particle size, other factors, such as maintenance of a suitable viscosity after dilution with a constant amount of water (which is important for oral gavage in rats), stability against creaming and phase separation, and the presence of an adequate amount of Phosal 50PG to solubilize the determined dose (10 mg/kg), were considered during the selection of the optimal formulation.

The physicochemical characteristics of the optimized formulations (PBF and PhytoSolve) appear in Table III. The results have demonstrated that PhytoSolve (−18.43±0.20) has higher zeta potential than PBF (−2.23±0.15), and PBF has significant smaller particle size than the PhytoSolve formulations. The percent transmittance data also indicated that PBF is more transparent than PhytoSolve. TEM analysis reveals spherical shapes and uniformity in the droplet size of the two new formulations (Fig. 3). The low PDI also confirmed uniformity of droplets.

HPLC Analysis

A reverse phase HPLC method was used to analyze the mebudipine concentration in the rat plasma. When detection was performed at 238 nm, the retention time of mebudipine was 11.9 min, and dibudipine, which was the internal standard, has a 22-min retention time. The calibration curve was linear over a range of 10–1,000 ng/mL with R^2=0.997. The extraction recovery was over 80% and no overlapping peaks were observed in the chromatograms. The lower limit of quantification (LLOQ) was 10 ng/mL, which is appropriate for pharmacokinetic studies in rats. The calculated inter- and intraday accuracy, as well as the precision for LLOQ (10 ng/mL), with 100, 500, and 1,000 ng/mL mebudipine as the low, medium and high concentrations are listed in Table IV.

Pharmacokinetic Studies

The curves corresponding to the plasma concentration of mebudipine over time following the oral administration of the four formulations (PhytoSolve, PBF, oily solution, and suspension) in rats are illustrated in Fig. 4, and the pharmacokinetic parameters are represented in Table V.

The results indicated that the C_{max} of PhytoSolve (81.0±20.7 ng/mL) and PBF (100.0±13.9 ng/mL) are significantly (p<0.001) higher than the other formulations, but the differences between the T_{max} values of all of the formulations were not statistically significant. The $AUC_{0\rightarrow 6\ h}$ (186.0±32.1 ng h^{-1} mL^{-1}) and $AUC_{0\rightarrow\infty}$ (218.6±39.9 ng h^{-1} mL^{-1}) of PBF were extremely significant (p<0.001) compared with the drug suspension and oily solution. The $AUC_{0\rightarrow 6\ h}$ (151.4±17.9 ng h^{-1} mL^{-1}) of PhytoSolve was extremely significant compared with the suspension (p<0.001) and oily solution (p<0.05); the $AUC_{0\rightarrow\infty}$ (186.9±31.3 ng h^{-1} mL^{-1}) of PhytoSolve was significantly higher

Table IV. Precision and Accuracy of Mebudipine Determination in Rat Plasma

Sample concentration (ng/mL)	10 (LLOQ)	100 (low)	500 (medium)	1,000 (high)
Intraday (n=5)				
Mean±SD	10.2±0.7	94.0±4.6	454.0±39.7	1,004.0±33.6
CV (%)[a]	7.3	4.9	8.7	3.3
Error (%)[b]	2.0	−6.0	−9.2	0.4
Interday (n=5)				
Mean±SD	9.6±0.4	95.2±4.1	459.0±45.0	985.0±45.3
CV (%)	3.7	4.3	9.8	4.5
Error (%)	−4.0	−4.8	−8.2	−1.5

LLOQ lower limit of quantification
[a] Precision (at each concentration) was expressed as CV%=(SD/ mean measured concentration)×100
[b] Accuracy (at each concentration) was expressed as the Error%, which was calculated by dividing the measured concentration minus the expected concentration to the expected concentration×100

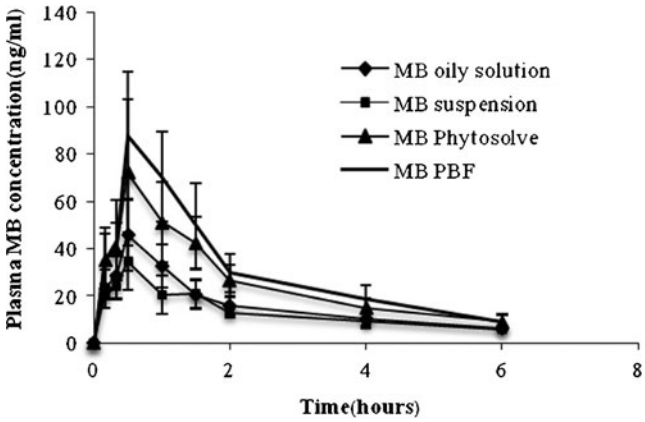

Fig. 4. Drug-concentration (mean±SD) over time profiles for various mebudipine (*MB*) formulations after oral administration to rats (n=6, dose=10 mg/kg)

($p<0.05$) than the corresponding values for the suspension and oily solution. The relative bioavailabilities of the mebudipine PBF and PhytoSolve with respect to the mebudipine suspension were found to be 234.58% and 191.63%, respectively.

DISCUSSION

In our study, male albino Wistar rats received single mebudipine doses (10 mg/kg) of different formulations orally to evaluate the formulations' effects on mebudipine's bioavailability.

The solubility studies indicated that the solubility of mebudipine in MCT oil was greater than in vegetable oils. Vegetable oils are mixture of triglycerides (TG) with complicated solubilizing behaviors and contain free fatty acid and other components. The long and bulky alkyl chains make TGs highly hydrophobic, while the ester region in the molecule causes high polarity. The effective concentration of the ester groups in TG determine the solvent capacity of TG for drugs; therefore, based on its weight, MCT has a higher solvent capacity compared with the long and bulky alkyl chain TG found in vegetable oils (18,19). Also, the unique structure of triglyceride molecules in vegetable oils can affect microemulsion formation and conventional surfactant are not able to produce low interfacial tension with vegetable oils without alcohol and co-oil addition (18). Phosal 53MCT is a better solvent for mebudipine than Phosal 50PG; however, the results of the stability studies have not materialized. Phosal 50PG has superior emulsifying capacity over Phosal 53MCT and is more miscible with water in the presence of glycerol. Phosal 50PG contains 50% phosphatidylcholine (PC) in propylene glycol (PG), lecithin, sunflower oil, and ascorbyl palmitate, as well as mono- and diglycerides. Phosal 53MCT consists of 53% PC in MCT, alcohol, glycerol stearate, oleic acid, and ascorbyl palmitate. The presence of the PG in Phosal 50PG leads to a more uniform formulation and prevents phase separation.

One of the properties of these formulations (PBF and PhytoSolve) is the formation of small particle sizes (PBF, 74.4 ±2.5 nm), while PhytoSolve particles are approximately 138.5 ±9.0 nm. Using probe sonicator instead of high pressured homogenizers causes an increase in the droplet size of PhytoSolve prepared in our laboratory when compared with the original PhytoSolve droplet size (30–60 nm), which was reported previously (9).

Polyols have some remarkable advantages compared with water as continuous phase in the field of o/w-emulsions. The influence on the interface between oil and polyol/water leads to a reduced interfacial tension and hence to lower diameters of the oil droplets compared with a pure water phase.

The zeta potential of the formulations was determined to predict the stability of the emulsions against aggregation in the environment where it will be used. However, the zeta potential of PBF is not negative enough, but it still demonstrates good stability during storage in room temperature and at 4 C. Other studies indicated that sometimes it is not possible to predict the stability of formulations based solely on the zeta potential values because the electrostatic stabilization is most likely not the main mechanism for the stability of these formulations (20).

The animal studies indicated that higher concentrations of mebudipine were achieved after the administration of the two novel formulations when compared with suspension and oily solution. The presence of the solvated drugs in small nanolipid globules (<150 nm) provides large interfacial areas for drug absorption. The emulsion droplet size is a very important characteristic because the rate and extent of drug release and absorption are dependent upon on it (11).

Previous studies have reported that PhytoSolve increases the bioavailability of coenzyme Q10 and vitamin E in healthy volunteers (10). Other studies have indicated that Sirolimus (12) and tumor-inhibiting Src kinase inhibitor TG100435, which are drugs formulated with Phosal 50PG, display higher levels of active ingredients in blood with better overall therapeutic effects (11). Phospholipids and particularly PC and its digestion

Table V. Pharmacokinetic Parameters Upon Oral Administration of Various Mebudipine Formulations

Pharmacokinetic parameters	Suspension	Oily solution	PBF	PhytoSolve
C_{max} (ng/mL)	37.8±8.8	49.8±12.9	100.0±13.9[a, c]	81.0±20.7[a, d]
T_{max} (h)	0.55±0.22	0.55±0.22	0.66±0.25	0.83±0.40
$T_{1/2}$ (h)	3.87±1.41	3.74±1.70	2.39±0.39	2.63±0.69
$AUC_{0\to6}$ (ng h^{-1} mL^{-1})	79.3±15.3	96.6±11.9	186.0±32.1[a, c]	151.4±17.9[a, d]
$AUC_{0\to\infty}$ (ng h^{-1} mL^{-1})	112.7±16.6	132.6±21.6	218.6±39.9[a, c]	186.9±31.3[b, d]

Data expressed as the mean±SD, n=6
[a] Significantly higher ($p<0.001$) compared with mebudipine suspension
[b] Significantly higher ($p<0.05$) compared with mebudipine suspension
[c] Significantly higher ($p<0.001$) compared with mebudipine oily solution
[d] Significantly higher ($p<0.05$) compared with mebudipine oily solution

product, lyso-phosphatidylcholine (LPC) also enhance lymphatic lipid transport and LPC has been shown to enhance the lymphatic transport of α-tocopherol and halofantrine (21). These results demonstrate that PC's could improve the absorption, effects, and therapeutic indices of drugs. Generally, phospholipids can be used as excipients in oral formulations to increase solubility of active substances, keep them solubilized in the GI tract, promote the drug absorption, and improve the bioavailability of these drugs (11). One of the key components of PhytoSolve and PBF are purified phospholipids. PC is being used to produce a wide variety of carrier systems improving the solubility, stability, and delivery of active pharmaceutical ingredients, such as mixed micelles, different types of liposomes, SLN, and many more. Its emulsifying properties are being used to produce self-emulsifying drug delivery systems or microemulsions for oral administration as well as emulsions for injectable use. The enhanced bioavailability of mebudipine is probably due to the presence of phospholipides in these formulation.

CONCLUSIONS

In conclusion, PhytoSolve and PBF raise the bioavailability of mebudipine significantly, relative to both its suspension and oily solution formulations, after oral administration. These new developments (PhytoSolve and PBF) are possible alternatives to conventional formulations for the oral delivery of lipophilic compounds with poor bioavailability.

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