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Research Paper

Development and oral bioavailability assessment of a supersaturated self-microemulsifying drug delivery system (SMEDDS) of albendazole

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Abstract

Objectives Albendazole's (ABZ) poor aqueous solubility is a major determinant of its variable therapeutic response (20–50%). The purpose of this study was to develop and optimize the composition of a self-microemulsifying drug delivery system (SMEDDS) of ABZ and assess its oral pharmacokinetics in rabbits.

Methods A D-optimal mixture design of experiments was used to select the levels of constraints of the formulation variables. The predicted composition was optimized using four responses: dispersion performance, droplet sizes, dissolution efficiency (DE) and time for 85% drug release ($t_{85\%}$).

Key findings The optimal composition of the ABZ-SMEDDS formulation, with approximately 5 mg/g drug loading of ABZ, was predicted to be Cremophor EL (30% w/w), Tween 80 (15% w/w), Capmul PG-8 (10% w/w) and acidified PEG 400 (45% w/w). An increase of 63% in the relative bioavailability compared with the commercial suspension was obtained with ABZ-SMEDDS as measured by albendazole sulfoxide (ABZSO) plasma levels. The area under the curve ($AUC_{0\rightarrow 24h}$) and the peak plasma concentration (C_{max}) of ABZ-SMEDDS was higher than those obtained with the commercial suspension by 56% and 52%, respectively.

Conclusions This study demonstrates a strategy for the development of a supersaturated SMEDDS formulation of a drug with low aqueous solubility.

Keywords albendazole; bioavailability; D-optimal design; microemulsion; self-microemulsifying drug delivery system (SMEDDS)

Introduction

Albendazole (ABZ) is a benzimidazole derivative with a broad spectrum of activity against human and animal helminth parasites.[1] ABZ is a poorly water-soluble drug (0.2 μg/ml in water at 25°C) and it has weak basic properties ($pKa_1 = 2.68$ and $pKa_2 = 11.83$) and a log P of 3.5.[2,3] Consequently, it is poorly and erratically absorbed from the gastrointestinal tract.[4,5] This property, which is ideal for its use against luminal infections, is a problem in the treatment of systemic helminthiasis.[6–8] Furthermore, the lack of water solubility reduces flexibility for drug formulation and administration. To overcome these drawbacks, increasing the aqueous solubility of ABZ is an important goal.

Different formulation approaches have been tried in the past to improve the aqueous solubility of ABZ. For instance, since ABZ is basic in nature, its solubility can be increased by ionization in an acid medium, although this increase in solubility is not sufficient for the preparation of high-ABZ-concentration formulations.[9] Another approach was by addition of surfactants, such as Tween 80 and bile salts, or cosolvent agents, such as Transcutol.[10–12] The use of liposomes[13] and a solid dispersion approach with polyvinylpyrrolidone[14–16] showed less promise. Recently, a formulation with a high concentration of ABZ was prepared by complexing with hydroxypropyl-β-cyclodextrin.[10,17,18] To our knowledge, there has not so far been any report of the application of a lipid delivery system, such as a self-microemulsifying drug delivery system (SMEDDS) for improving the solubility of ABZ. This is primarily because of ABZ's low solubility in commonly used surfactants and oils,[10] which makes the lipid formulation approach rather challenging.

Self-microemulsifying drug delivery systems (SMEDDS) are a promising technology for improving the rate and extent of the absorption of poorly water-soluble drugs.[19–22]

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A SMEDDS is a mixture consisting of drugs, oils, surfactants and co-surfactants. Therefore, development of such a system can be complicated, as drug loading is a critical formulation design factor that is dependent on the drug solubility in various formulation components. In general, excipients with higher solubilizing efficiency are selected for formulation development. However, the most important factor for these formulations to be successful *in vivo* is that the formulation should be capable of preventing any precipitation of the drug after release for long enough to permit absorption. In this study, an attempt has been made to build a model to screen commonly used solubility-enhancing excipients. This should ensure not only the actual drug loading capacity of the formulation, but also its physical and chemical stability.

This research aimed to find an efficient way to develop a SMEDDS formulation for ABZ. It has been reported that ABZ's solubility coefficient increases as the pH decreases.[10,23] Based on this observation, our formulation development strategy involved a supersaturation step, where polyethylene glycol 400 (PEG 400), a non-ionic organic solvent, was acidified with concentrated hydrochloric acid (HCl) to dissolve ABZ, which was then incorporated into the SMEDDS. A D-optimal mixture design was used to optimize ABZ-SMEDDS formulation with high drug concentration. The chemical and thermodynamic stability of the optimized formulation was then determined under accelerated conditions. Finally, a pharmacokinetic evaluation was performed to find out the oral bioavailability of the supersaturated ABZ-SMEDDS in rabbits and this was compared with a commercially available ABZ suspension, Zentel® (GlaxoSmithKline, USA).

Materials and Methods

Materials

The chemical structure of ABZ is shown in Figure 1. Albendazole was purchased from Sigma (St Louis, MO, USA). Plurol Oleique CC497 (polyglyceryl oleate), Labrasol (caprylocaproyl macrogolglycerides), Labrafac Lipo WL1349 (medium chain triglycerides), Labrafil M1944 CS (oleoyl macrogolglycerides) and Transcutol HP (diethylene glycol monoethyl ether) were provided by Gattefosse, France. Capmul PG-8 (propylene glycol monocaprylate), Capryol PGMC (propylene glycol monocaprylate), Caprol PGE-860 (decaglycerol mono-, di-oleate), Captex 200 (propylene glycol dicaprylate/dicaprate) and Acconon CC-6 (polyoxyethylene 6 caprylic/capric glycerides) were obtained from Abitec Corporation (Columbus, OH, USA). Cremophor EL (castor oil, ethoxylated), Pluronic L101 (polyoxyethylene-polyoxypropylene block co-polymer), Cremophor PS 20 ester (20 mole ethoxylate of sorbitan mono laurate) were obtained from BASF (Mount Olive, NJ, USA). Tween 80 (polysorbate 80), PEG 400 (polyethylene glycol 400), SPAN 80 (sorbitan monooleate), cottonseed oil, corn oil, olive oil, peppermint oil, castor oil, light mineral oil and soyabean oil were purchased from Fisher Scientific (Pittsburgh, PA, USA). All other chemicals used were of analytical grade.

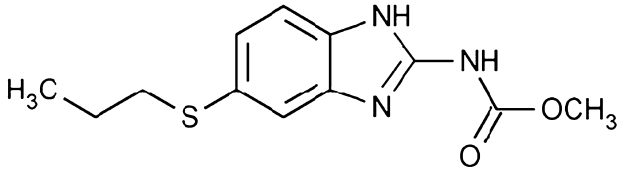

Figure 1 The structure of albendazole (methyl [5-(propyl-thio)-1-H-benzimidazole-2yl]carbamate).

Screening of oils and surfactants

The solubility study was carried out in two parts. In part one, ABZ was added in excess quantity to each of the excipients listed in Table 1. After 72 h of shaking at room temperature, tubes were centrifuged at 12 000 RPM for 15 min. The supernatant from each tube was filtered through a 0.45 μm filter and analyzed using an HPLC method as reported in the literature.[24]

In part two, a previously reported method was followed with certain modifications.[25] A fixed amount of each of the excipients was placed in a 20 ml glass vial with excess drug. A 1 : 1 mixture of 2-propanol and tetrahydrofuran (THF) sufficient to dissolve the drug : excipient mix was added to each vial. These were then agitated until the drug was fully dissolved. Each vial was kept in a vacuum oven at 2.5 psig and 40°C for 5 days to remove the solvents. All vials were re-weighed and kept at room temperature overnight to equilibrate. Next day, 5 ml of water was added to each vial and mixed for 2 h at room temperature. The contents of each vial were centrifuged at 12 000 rpm for 15 min. Supernatants were half diluted with a 1 : 1 mixture of 2-propanol and THF

Table 1 Equilibrium solubility of albendazole in various excipients and water

Excipients	ABZ solubility in excipients (mg/g)	ABZ solubility in water (mg/ml)
Plurol Oleique CC 497	0.089 ± 0.004	0.000
Cremophor EL	1.481 ± 0.045	0.755 ± 0.010
PEG 400	1.400 ± 0.023	0.008 ± 0.001
Sorbitan monooleate (SPAN 80)	0.748 ± 0.010	ND
Cottonseed oil	0.067 ± 0.002	0.001 ± 0.000
Corn oil	0.062 ± 0.002	0.001 ± 0.000
Olive oil	0.082 ± 0.003	0.001 ± 0.000
Peppermint oil	0.000	0.000
Castor oil	0.548 ± 0.012	0.001 ± 0.000
Light mineral oil	0.000	0.000
Tween 80	1.311 ± 0.008	0.586 ± 0.020
Caprol PGE-860	0.319 ± 0.016	ND
Acconon CC-6	1.392 ± 0.022	0.237 ± 0.011
Capmul PG-8	1.463 ± 0.031	0.000
Pluronic L101	0.264 ± 0.004	ND
Capryol PGMC	1.126 ± 0.008	0.000
Labrasol	1.398 ± 0.011	0.114 ± 0.002
Labrafac Lipo WL 1349	0.246 ± 0.005	0.002 ± 0.000
Transcutol HP	2.862 ± 0.017	0.008 ± 0.000
Labrafil M 1944 CS	0.562 ± 0.007	ND
Cremophor PS 20 ester	1.267 ± 0.013	0.318 ± 0.002
Soyabean oil	0.019 ± 0.003	0.001 ± 0.000
Captex 200	0.230 ± 0.002	0.001 ± 0.000

ABZ, albendazole; ND, not done. Mean ± SD, $n = 3$.

Table 2 Component ranges in the D-optimal mixture design

Component	Range (%)
X1	30–70
X2	30–70
X3	0–10

to prevent any further precipitation and eliminate residual turbidity. Samples were analyzed by HPLC.

Effect of acidified polyethylene glycol 400 on albendazole solubility

PEG 400 solutions of different concentrations (10, 20, 30, 40, 50, 60, 70, 80, 90 and 100% w/w) were prepared in pH 2.0 buffer solution (NaCl/HCl/glycine). Each solution was then acidified with different percentages of concentrated HCl (1, 3, 5, 7 and 9% w/w). Excess ABZ was added to these solutions and the drug solubility was evaluated as described above.

Construction of a pseudo-ternary phase diagram

The pseudo-ternary phase diagram was constructed by titration of homogeneous liquid mixtures of oil (Capmul PG-8), surfactant (Cremophor EL) and cosurfactant (Tween 80) with water at room temperature. For each phase diagram, a surfactant/cosurfactant (S/CoS) blend mixed at a specific ratio, such as 2 : 1, 3 : 1 or 4 : 1, was used. At each ratio of S/CoS, the proportions of oil and S/CoS blend in the mixture was varied from 9 : 1 to 1 : 9. Water was added drop by drop, under magnetic stirring, to each oily mixture. Then each mixture was visually observed for changes from turbid to transparent and back again.

Experimental design

A Design Expert® (version 7.1, Stat-Ease, Inc., Minneapolis, MN, USA) was used to generate the D-optimal mixture design. The mixture studied was a three-component system: a mixture of Cremophor EL, surfactant (S) and Tween 80, cosurfactant (CoS) (S : CoS = 2 : 1, w/w) (X1), acidified PEG 400 (X2) and Capmul PG-8 (X3). Based on the solubility studies and pseudo-ternary phase diagrams, the range of each component was selected as shown in Table 2.

The base design allowed 16 experiments for the fitting of a cubic model, a check for lack of fit and an estimate of experimental error in the solubility of ABZ in the formulations, as shown in Table 3.

The predicted composition was optimized using several responses: dispersion performance in simulated intestinal fluid (SIF, 0.05 M phosphate buffer, pH 6.8), microemulsion droplet sizes, $t_{85\%}$ (85% release at 30 min) in phosphate buffer (pH 6.8) and dissolution efficiency (DE). The latter figure was calculated using the following equation:

$$\text{dissolution efficiency (DE)} = \frac{\int_0^t y\,dt}{y_{100} \times t}$$

where DE represents the area under the dissolution curve up to a certain point t, expressed as a percentage of the area of the rectangle described by 100% dissolution (y_{100}) in the same time and y is the cumulative percentage of drug released.[26]

Droplet size measurements

SMEDDS (1 ml) was diluted 10 times and 100 times with distilled water in a beaker with constant stirring with a magnetic stirrer. The droplet size distributions of the resultant microemulsion was determined after 1 h by dynamic light-scattering spectroscopy using a Zetasizer Nano S (Malvern Instruments, UK). All studies were repeated three times and the average values were used.

Stability studies

The thermodynamic stability was evaluated by the phase separation on 1 : 10, 1 : 50, 1 : 100 and 1 : 500 dilution followed by centrifugation at 4000 rpm for 20 min and subsequent any change in droplet sizes. To evaluate the effect of temperature, the formulation was subjected to freeze–thaw cycles (–20°C for 2 days followed by +40°C for 2 days). At the end of the cycle, the formulation was diluted and centrifuged as described above and phase separation and the change in droplet size were determined.

Oral bioavailability study

Experiments were performed on six New Zealand white female rabbits, 2.5–3.5 kg, with a 14-day wash-out period between doses. Rabbits were fasted for 24 h before the study, but water was freely available. For intravenous administration, a solution (5 mg/ml) of ABZSO in dimethylsulphoxide was injected through the ear marginal vein (1 mg/kg). The same rabbits were given a single oral dose (10 mg/kg) of ABZ in either SMEDDS (5 mg/g) or a commercial suspension, Zentel® (40 mg/ml). One milliliter of blood was collected in duplicate from each rabbit through the ear vein at every sample time point. Samples were prepared by a previously published method.[27] The HPLC method for the determination of ABZ, albendazole sulfoxide (ABZSO), albendazole sulfone (ABZSO2) and phenacetin (internal standard) in rabbit plasma was also developed by following a prior method.[28] Briefly, a solution of 1.25% triethylamine in water–methanol–acetonitrile (72 : 15 : 13, v/v/v) was adjusted to pH 3.1 using 85% o-phosphoric acid. This was then used as the mobile phase. Chromatography was performed using Water's Alliance 2795 system and a Hypersil® ODS C18 column (250 mm × 4.6 mm, 5 μm). Mobile phase flow rate was 1.0 ml/min.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters were obtained by a non-compartmental analysis using WinNonlin® (version 5.2, Pharsight, Mountain View, CA, USA) pharmacokinetic software. The $AUC_{0\rightarrow 24h}$ is the area under the plasma concentration–time curve from time 0 to the time of the last observed concentration after an oral dose (24 h), as calculated using the linear trapezoidal rule. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were directly obtained from plasma data. Data are presented as means ± standard deviation (SD) and where applicable, the differences among groups were analyzed by Student's t-test

Table 3 Three-component mixture design and results

Run	Cremophor EL/Tween 80 mixture (%)	Acidified PEG 400 (%)	Capmul PG-8 (%)	Solubility (mg/g)
4	30.00	60.00	10.00	4.000 ± 0.024
11	38.75	53.75	7.50	3.150 ± 0.017
16	50.00	50.00	0.00	1.040 ± 0.030
5	60.00	30.00	10.00	4.561 ± 0.011
3	30.00	65.00	5.00	1.300 ± 0.011
7	45.00	45.00	10.00	5.075 ± 0.023
1	50.00	50.00	0.00	0.970 ± 0.012
6	30.00	70.00	0.00	0.130 ± 0.008
12	30.00	70.00	0.00	0.136 ± 0.009
8	58.75	38.75	2.50	1.150 ± 0.021
2	70.00	30.00	0.00	0.176 ± 0.010
10	65.00	30.00	5.00	1.275 ± 0.007
13	70.00	30.00	0.00	0.181 ± 0.011
15	30.00	60.00	10.00	3.988 ± 0.005
14	60.00	30.00	10.00	4.405 ± 0.012
9	38.75	58.75	2.50	0.852 ± 0.006

Mean ± SD, $n = 3$.

and non-parametric Kruskal–Wallis one-way analysis of variance. A P value less than 0.05 was considered statistically significant.

Results and Discussion

Screening of oils and surfactants

Non-ionic surfactants were used in this study since they are known to be less affected by pH and changes in ionic strength.[26] The results of solubility studies on ABZ in various oils and surfactants are presented in Table 1. It is very clear from the data obtained that ABZ does not have good solubility in any of the excipients used. The highest solubility was 2.862 mg/g in Transcutol HP. These results concur with those of Torrado *et al*.,[10] who found low solubility of ABZ in similar solubility enhancers.

Some excipients showed relatively high solubilizing ability, for example Cremophor EL (1.481 mg/g), Capmul PG-8 (1.463 mg/g) and Tween 80 (1.311 mg/g) were identified from the list. However, in the solubility studies in water with the intimate mixtures of ABZ and each of these excipients, it was revealed that drug crystallized out of the solution for most of the excipients.

Cremophor EL and Tween 80 showed an enhancement of aqueous solubility of ABZ to 0.755 mg/ml and 0.586 mg/ml, respectively. Based on these results, Cremophor EL and Tween 80 were selected for SMEDDS formulation development. Although Capmul PG-8 showed no improvement on ABZ's solubility in water its high drug-loading capacity favored selection as the oil phase.

Effect of acidified PEG 400 on albendazole solubility

The solubility of ABZ was evaluated as a function of the percentage of PEG 400 acidified with concentrated HCl, as shown in Figure 2. The solubility data revealed that concentrated HCl caused a major supersaturation of ABZ. The solubility also increased as PEG 400 concentration increased. The highest supersaturation solubility of ABZ was between 10.4 and 12.5 mg/g in 90–100% w/w PEG 400 acidified with 5% w/w concentrated HCl. These results are favored by the fact that the solubility of ABZ is known to follow pseudo-first-order kinetics and the solubility of ABZ increases as the pH decreases.[10] The sudden drop in solubility with a concentrated HCl level of more than 5% w/w can be explained by supersaturation of ABZ in the system, which, on mixing, precipitates out of the system.

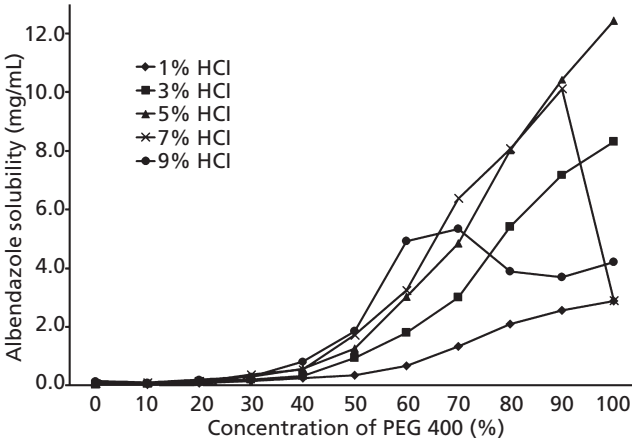

Figure 2 Solubilities of albendazole at different percentages of acidified PEG 400.

Construction of pseudo-ternary phase diagram

It was observed that increasing the concentration of the CoS (Tween 80) within the self-microemulsifying region causes increased spontaneity of the self-microemulsification process. When a CoS was added to the system, it further lowered the

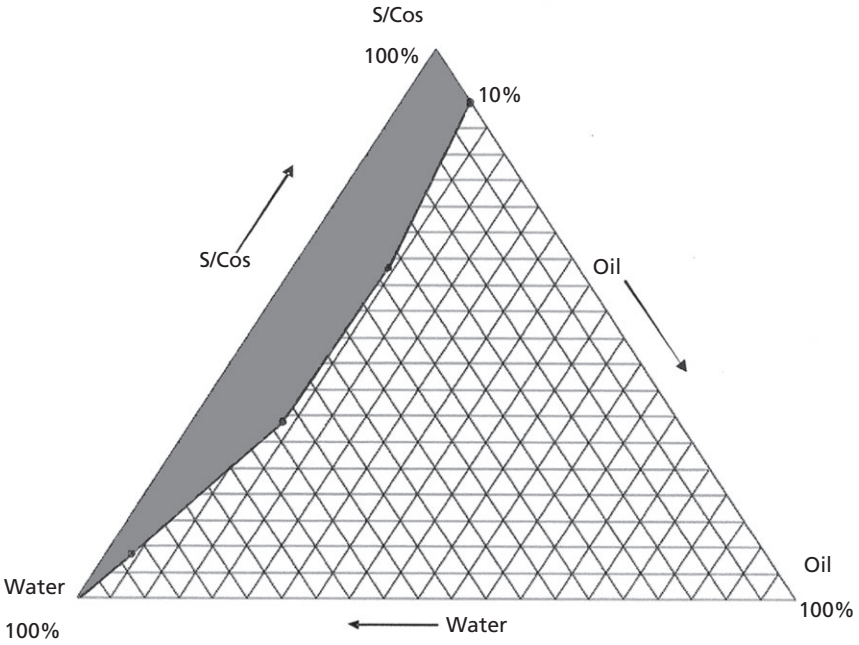

Figure 3 Pseudo-ternary phase diagram of formulation composed of Cremophor EL: Tween 80 : Capmul PG-8 dispersed in water. S : CoS, 2 : 1. The shaded area represents the oil-in-water microemulsion.

Table 4 Experimental design for optimization and results

Run	Cremophor EL/Tween 80 Mixture (%)	Acidified PEG 400 (%)	Capmul PG-8 (%)	Droplet size (nm) (mean ± SD, $n = 3$)	$t_{85\%}$ (min) (mean ± SD, $n = 6$)	DE (%) (mean ± SD, $n = 6$)	Turbidity
15	40.00	48.00	12.00	198.2 ± 25.7	4.5 ± 1.6	96.94 ± 1.05	2
5	40.00	48.00	12.00	202.8 ± 19.4	7.9 ± 2.1	95.75 ± 3.02	2
7	47.50	42.50	10.00	25.8 ± 5.6	11.8 ± 0.8	93.11 ± 1.18	1
6	48.00	40.00	12.00	221.0 ± 23.9	9.7 ± 1.2	93.83 ± 1.00	2
4	50.00	40.00	10.00	38.8 ± 3.7	5.0 ± 1.8	96.39 ± 1.61	1
13	42.00	50.00	8.00	125.3 ± 11.1	4.7 ± 0.5	96.50 ± 2.55	2
11	44.00	44.00	12.00	188.6 ± 33.4	10.5 ± 2.8	93.67 ± 1.75	2
16	48.00	40.00	12.00	209.3 ± 53.7	9.2 ± 3.3	95.11 ± 3.33	2
12	40.00	50.00	10.00	37.2 ± 10.9	8.5 ± 1.5	94.53 ± 2.01	1
3	50.00	42.00	8.00	151.7 ± 17.8	8.1 ± 2.5	95.44 ± 2.48	2
9	40.00	50.00	10.00	35.1 ± 5.9	10.0 ± 3.4	93.44 ± 1.77	1
14	50.00	42.00	8.00	139.2 ± 23.7	9.5 ± 1.0	94.06 ± 2.08	2
1	45.00	45.00	10.00	15.8 ± 0.8	7.9 ± 2.3	95.44 ± 3.43	1
8	42.50	47.50	10.00	24.6 ± 1.6	4.7 ± 1.5	96.67 ± 1.09	1
10	46.00	46.00	8.00	105.6 ± 21.1	9.4 ± 2.2	94.50 ± 1.43	2
2	42.00	50.00	8.00	124.3 ± 32.1	9.0 ± 4.2	94.83 ± 2.30	2

interfacial tension between the oil and water interface, and also influenced the curvature and stability of the interfacial film, therefore the S/CoS ratio was selected as 2 : 1 and the efficiency of microemulsification was good when the S/CoS concentration was between 90 and 100% w/w of the formulation, as shown in Figure 3. The concentration of Capmul PG-8 was found to be suitable for concentrations less than 10% w/w of the formulation.

Experimental design

Phase studies were performed to define the restricted domain of the experimental design. This SMEDDS forms an oil-in-water microemulsion with gentle stirring on being introduced into aqueous media. Different concentrations of acidified PEG 400 solutions containing 5% (w/w) concentrated HCl were incorporated in the mixture design to estimate their effect on the solubility. The domain was defined according to the proportions of the surfactant, cosurfactant and oil in the microemulsion region.

Table 3 shows the results from the 16 experiments in terms of ABZ equilibrium solubility. It should be noted that a SMEDDS equilibrated with excess solid drug was obtained after centrifugation and before analysis. This shows that the presence of ABZ does not affect the stability of SMEDDS and

that the system was saturated with ABZ. As shown in Table 3, the wide variation of response indicates that the different compositions result in different drug solubilities.

Analysis of the response variables was carried out using experimental design software. The cubic model was found most suitable to approximate to the response values, due to its small standard deviation of 0.051 and predicted residual sum of squares (PRESS) of 0.17, as well as its large predicted R-squared value of 0.9966. The *P* value of the lack of fit of the model was 0.6296, which implies that the lack of fit is not significant relative to the pure error.

Optimization of SMEDDS formulation

A careful characterization of the ABZ-SMEDDS formulation is required for its optimization. The mixture design experiments helped to optimize the formulation to avoid drug precipitation.

Mixture experiments are defined as an experiment where the response is assumed to depend only on the relative proportions of the components present in the mixture and not on the amount of the mixture itself. This is what is expected for the SMEDDS. In this design, a 2 : 1 mixture of Cremophor EL and Tween 80 (45 ± 5% w/w) was mixed with acidified PEG 400 (45 ± 5% w/w) and Capmul PG-8 (10 ± 2% w/w). A total of 16 combinations were created. Each of these formulations contained a fixed ABZ concentration of 5 mg/g. Four response variables were used to optimize the formulations. The generated design points with their response values are summarized in Table 4. SMEDDS was diluted with SIF to determine whether these systems could form microemulsions with the external phase of the system without phase separation. The turbidity of the aqueous dispersion was assessed visually in a qualitative manner by assigning 1 and 2 for clear and turbid, respectively. Droplet sizes were measured and the optimum range was found to be less than 50 nm.

The droplet size was significantly influenced by the level of Capmul PG-8 and also the ratio between S/CoS and acidified PEG 400. As expected, the turbidity on dilution was similarly influenced by the level of oil in the formulation. The lowest droplet size was found to have an oil level of 10% w/w.

Dissolution studies for SMEDDS containing ABZ were performed according to the design points to evaluate the effects of the droplet size on the release profiles. These in turn determined the effects of formulation components. The release of ABZ from these formulations was evaluated in 0.05 M phosphate buffer (pH 6.8) and the profiles are presented in Figure 4. The release profiles were characterized by $t_{85\%}$ and dissolution efficiency (DE). Pharmacopoeias very frequently use the $t_{85\%}$ parameter as an acceptance limit of the dissolution test. US-FDA guidance for immediate-release products suggests that 85% ($t_{85\%}$) of the labeled amount of drug should release within 30 min of the dissolution study.[29]

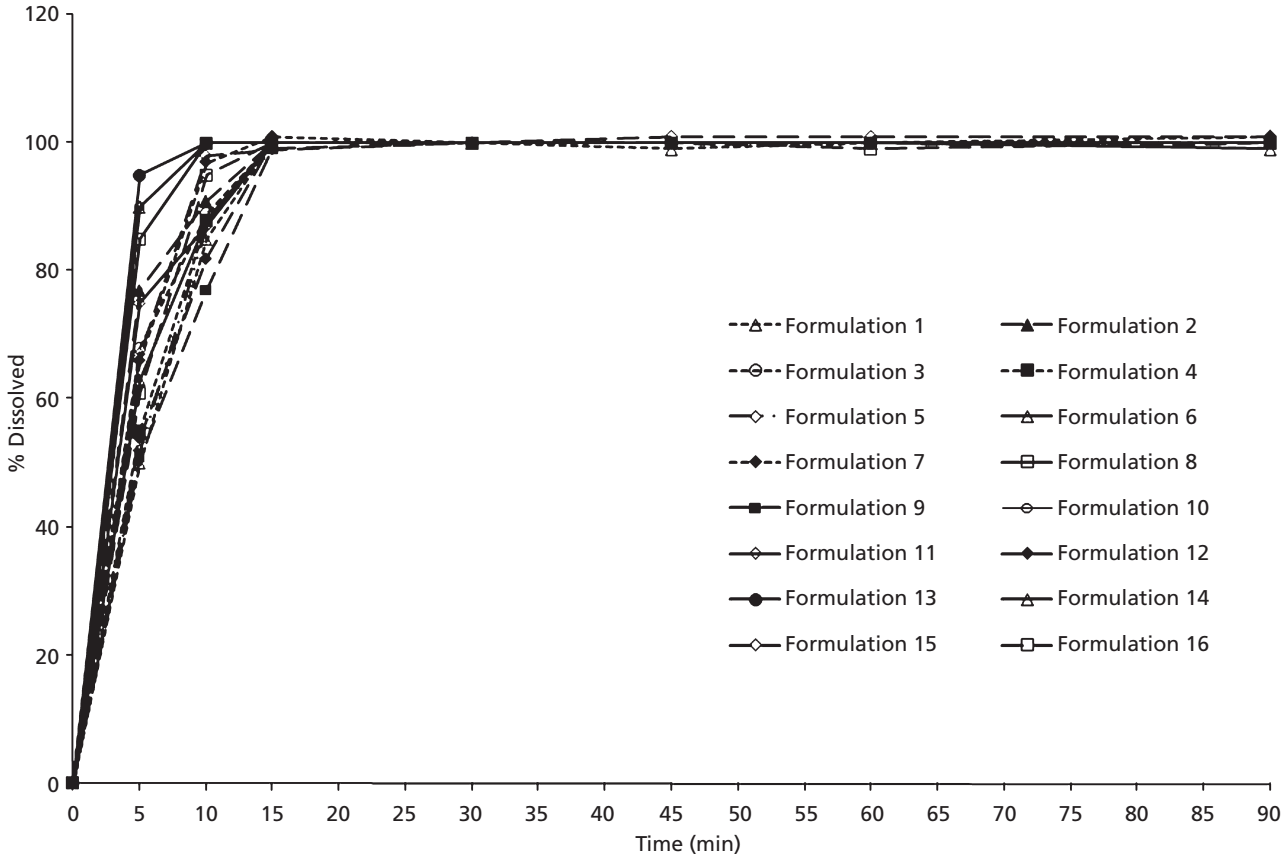

Figure 4 Dissolution profiles of albendazole from the SMEDDS formulation in phosphate buffer at pH 6.8.

Table 5 Verification of model prediction

Test point	Percentage of components				Solubility (mg/g) (mean ± SD, $n = 3$)		Droplet size (nm) (mean ± SD, $n = 3$)		$t_{85\%}$ (min) (mean ± SD, $n = 6$)		DE (%) (mean ± SD, $n = 3$)	
	Cremophor EL	Tween 80	Acidified PEG 400	Capmul PG-8	Predicted	Measured	Predicted	Measured	Predicted	Measured	Predicted	Measured
1	26.67	13.33	50.00	10.00	4.82	4.88 ± 0.35	34.8	40.5 ± 6.6	7.4	8.2 ± 0.4	95.32	96.21 ± 2.22
2	28.00	14.00	50.00	8.00	3.65	3.91 ± 0.14	125.2	140.5 ± 41.9	7.5	7.7 ± 1.2	95.26	94.29 ± 1.95
3	32.00	16.00	44.00	8.00	3.83	3.28 ± 0.21	123.2	132.6 ± 30.7	8.4	7.8 ± 0.9	94.86	95.22 ± 2.02

Table 6 Droplet size results upon dilution

Dilution	Mean droplet size (nm)
1/10	86.1 ± 3.5
1/50	112.2 ± 10.3
1/100	383.4 ± 23.6
1/500	423.3 ± 20.4

In our study the DE of SMEDDS varied from 93.11 to 96.94% while $t_{85\%}$ varied between 4.5 and 11.8 min. The $t_{85\%}$ and DE were most affected by the levels of S/CoS and acidified PEG 400. There was no noteworthy effect of the level of Capmul PG-8 on the dissolution characteristics of the formulations. A 45% w/w S/CoS mixture with 45% w/w acidified PEG 400 produced the desired dissolution profile. The response variables of the optimized formulation were experimentally determined in triplicate and the results are shown in Table 5. Three formulations of different compositions satisfying these criteria were prepared and evaluated. Good agreement was obtained between the model prediction and experimental observation.

Stability studies

No phase separation of the ABZ-SMEDDS formulation was observed on centrifugation. However, the thermal cycling study created a thermodynamically unstable microemulsion, which had a larger droplet size distribution on dilution. The mean droplet sizes are reported in Table 6. This study reveals that a sudden change in temperature causes a change in entropy of the system, which results in coalescence of the droplets. The overall stability of the formulation under normal conditions was found to be acceptable.

Oral bioavailability study

After oral administration, unmodified ABZ was not detected in any of the plasma samples. This is in accordance with the results obtained by other authors in different animal species.[30–32] The main two metabolites are the S-oxidation compounds (ABZSO and $ABZSO_2$). As ABZSO has also anthelmintic properties,[33] the bioavailability characteristics of ABZ were assessed from the plasma concentrations of ABZSO obtained after administration of the two dosage forms. The kinetics of ABZ absorption in the GI tract follows a passive diffusion process[34] and is independent of the administered dose.

Mean concentration–time profiles of ABZSO obtained after a single dose (10 mg/kg) of ABZ SMEDDS and the ABZ commercial suspension are reported in Figure 5. The different pharmacokinetic parameters are shown in Table 7. They were calculated as the mean of the experimental data. The C_{max} and $AUC_{0\rightarrow 24h}$ of ABZ-SMEDDS were significantly higher than those of the commercial suspension, with a 52% increase in the C_{max} value ($P = 0.019$) and a 56% increase in $AUC_{0\rightarrow 24h}$ ($P = 0.0009$).

The enhancement of bioavailability is generally ascribed to the increase in solubility and dissolution rate of the drug due to microemulsion formation. However, the drug absorption rate itself may be decreased because only the free drug can be absorbed. In the case of ABZ, the microemulsion seems to be

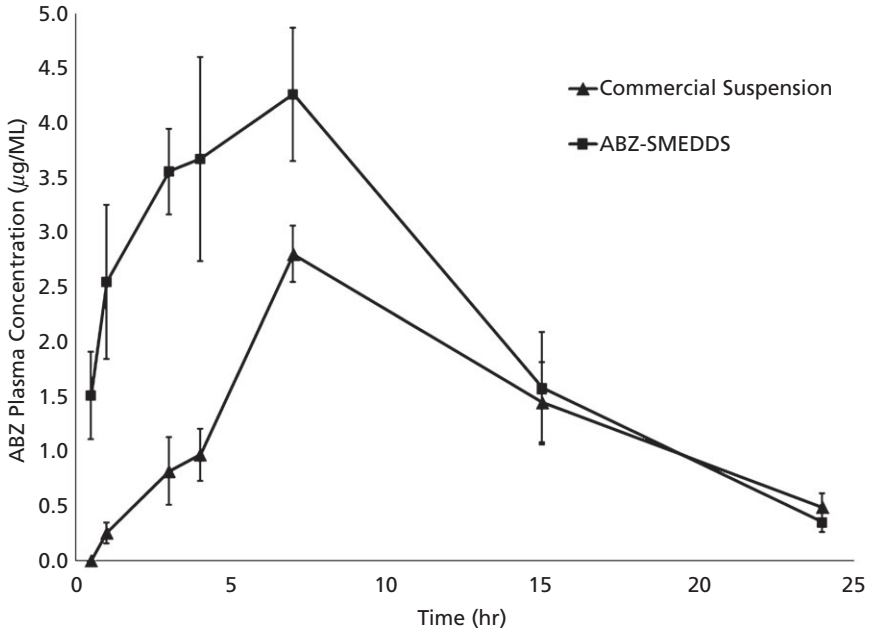

Figure 5 Plasma concentration profile of albendazole after oral administration of SMEDDS formulation and a commercial suspension. Adminstration in rabbits, 10 mg/kg, $n = 6$.

Table 7 Pharmacokinetics parameters for ABZSO obtained following oral administration of ABZ to rabbits

Parameters	ABZ-SMEDDS	Commercial suspension
C_{max} (μg/ml)	4.3 ± 0.6	2.8 ± 0.3
$AUC_{0\rightarrow 24h}$ (μg.h/ml)	54.6 ± 0.5	33.4 ± 3.2
Bioavailability (%)	80.2 ± 8.4	48.8 ± 4.7

10 mg/kg bodyweight of ABZ administered to rabbits, $n = 6$. Mean ± SD.

sufficiently labile to release free ABZ. In view of these results, the SMEDDS is a good alternative for treatment of systemic helmintic diseases, increasing the gastrointestinal absorption of the drug and reducing the inter- and intra-individual variability.

Conclusions

This study demonstrates a mathematical and statistical approach that can be used to obtain a superior experimental mixture design when the experimental factor space is not a simplex space. By applying a one-factor-at-a-time approach, it would have been extremely challenging, if not impossible, to achieve the objectives of optimization for such a complex system. The optimal composition of ABZ-SMEDDS formulation with approximately 5 mg/g drug load was predicted to have 30% w/w of Cremophor EL, 15% w/w of Tween 80, 45% w/w of acidified PEG 400 (containing 5% w/w concentrated HCl) and 10% w/w Capmul PG-8. This study has provided an efficient model for formulation component selection that allows identification of the excipients and the loading levels that generate the highest and most stable kinetic solubility on dilution. The use of acidified PEG 400 as a cosolvent in the formulation is a unique approach towards solving issues with high drug loading. After oral administration of 10 mg/kg ABZ to six rabbits, the oral bioavailability of the SMEDDS formulation was 63% greater than that of the commercial suspension. Our study indicates that the use of SMEDDS for the oral delivery of ABZ may be an option to improve its systemic availability.

Declarations

Conflict

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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