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Formulation parameters of albendazole solution

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Abstract

The solubility of albendazole, a poorly water-soluble drug was evaluated. The effect of cosolvents and pH on the aqueous solubility of albendazole are described here. Albendazole aqueous solubility was tested over the pH range of 1.2–7.5. Albendazole solubility was lower for the highest pH values. The solubility coefficient obtained was 0.376 mg/ml in a 1.2 pH buffer solution. Transcutol was the cosolvent with which the increase of the solubility was highest. Albendazole solubility at different percentages of transcutol presented a sigmoid kinetic with an initial acceleration phase. This kinetic shows an exponential correlation for transcutol values smaller than 80%. The exponent value (n) was higher as the pH of the solution was increased. This high value of the exponent (n) is due to a stronger influence of the transcutol on the solubility of albendazole at elevated pH values. The albendazole solution containing 40% w/w of transcutol in a pH 1.2 buffer solution was selected because of its high solubility (2.226 mg/ml). Analysis of the stability data of this albendazole solution showed good correlation ($r = 0.9831$) when the data were fitted to a first order equation. This albendazole solution showed good stability, with less than 10% degradation occurring after 30 days of storage at 4°C.

Keywords: Albendazole; Solvent system; Transcutol; Surfactant

1. Introduction

The main treatment used for human hydatidosis is surgery. Surgical treatment for cystic hydatid disease patients commonly involves endocystectomy and endocystectomy with puncture, aspiration, administration of protoscolicide and respiration (PAPR) (Wen et al., 1993). Oral administration of albendazole or other antihydatid drugs should be also considered before and after surgery for the prevention of hydatid recurrence after surgical treatment (Wen et al., 1989). Experience with albendazole indicates that the poor water solubility of albendazole cause a great variability on its absorption in hydatid patients.

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Thus, a key point is how to increase the oral bioavailability of albendazole (Wen et al., 1993).

The use of solvent systems in order to raise the solubility and bioavailability of poorly soluble drugs has been studied extensively (Poelma et al., 1990; Mackellar et al., 1994). Intestinal absorption of albendazole using differents surfactants was studied by Estal et al., 1993.

The aim of this work was to improve the bioavailability of albendazole by increasing its solubility through the addition of cosolvents over a wide pH range. The stability of the albendazole solution was also evaluated.

2. Materials and methods

2.1. Materials

Albendazole was supplied by Smithkline Beecham Pharmaceuticals, England, via S.K.B., Spain. Transcutol (diethylene glycol monoethyl ether) a liquid miscible with both water and oils was furnished by Gattefosse Corp. (Madrid, Spain). All other ingredients were of pharmaceutical grade.

2.2. Solubility determination

Solubility (w/w) at 24°C was determined using the shaker method (Yu et al., 1994). An excess of the compound was placed in solvent in a screw-capped glass tube, connected to a wrist-action flask shaker, immersed in a water bath maintained at the required temperature, and agitated continuously for >24 h. Albendazole samples were analyzed in a Beckman DU6 spectrophotometer at 291 nm in a pH 1.2 buffer.

All solubility measurements were performed in triplicate.

2.3. Effect of pH on the albendazole solubility

Different buffer solutions (pH 1.2 (KCl/HCl), 2.0 (NaCl/HCl/glycine), 3.5 (NaCl/HCl/glycine), 4.0 (NaCl/acetic acid/sodium acetate), 5.0 (NaCl/acetic acid/sodium acetate), 6.0 (NaCl/disodium hydrogen phosphate/sodium dihydrogen phosphate) and 7.5 (NaCl/disodium hydrogen phosphate/sodium dihydrogen phosphate) were used. All these buffer solutions had the same ionic strength (0.3) obtained by the addition of NaCl. The pHs of the filtered solutions were measured and the albendazole concentrations were evaluated after the shaker method. (Formation of mixed solvent systems.)

2.4. Effect of solubility enhancers

The surfactants and cosolvents Cremophor EL, Tween 20, sodium lauryl sulfate and transcutol were assessed for their ability for enhance the solubility of albendazole in aqueous phase. An accurate weight of material was taken to obtain a solution with a concentration of 5% w/w of solubility enhancer in 1.2 pH buffer solution.

2.5. Effect of pH range on different transcutol solutions

An accurate weigh of transcutol was taken and the different percentages (w/w) of transcutol (0, 5, 20, 40, 60, 80, 100%) were prepared in each of the three buffer solutions to obtain the different mixed solvent systems.

Excess albendazole was added to these systems, and the drug concentrations were evaluated after the solubility study.

2.6. Stability studies

Accelerated stability studies were carried out on albendazole solution formulations. The storage containers were glass bottles with screw caps fitted with teflon cap liners. The samples were stored at 4, 25, 45 and 70°C for appropriate periods of time depending on the decomposition rate.

2.7. High-performance liquid chromatography (HPLC)

Albendazole concentrations were determinated by HPLC. The method employed mebendazole as internal standard. Methanol was used for dilution and cleaning up the samples. A Gilson chromatographic system consisting of a pump (mod. 305),

Isochrom solvent delivery system (mod. 811B), Rheodyne valve injector (mod. 231XL), variable-wavelength uv absorbance detector (mod. 116) and SP 4270 integrator was employed. Chromatography was carried out using a Lichrosorb RP 18, 10 μm (Merck Co., Darmstadt, Germany); 200 X 4.6 mm I.D. reverse-phase column. The column was eluted with methanol-water (60:40 v/v), and the eluent was run at a rate of 1.0 ml/min and monitored at 291 nm. The injection volumes for the albendazole sulphone solutions were of 20 μl. The calibration curve was found to be linear in the range of 0–150 μg/ml. The HPLC method was stability-indicating. The results were analyzed by linear regression and almost all the curves showed a correlation coefficient of 0.9991.

3. Result and discussion

Fig. 1 shows a graph of the albendazole solubility coefficient versus pH. The albendazole solubility coefficient increases as the pH decreases. Albendazole solubility is 0.376 mg/ml in a 1.2 pH buffer in contrast to the solubility of 0.016 mg/ml in a 6.0 pH buffer solution which is the lowest concentration achieved. It is evident that the solubility of albendazol follows a pseudo-first-order kinetic.

The solubilities coefficients for 5% solutions of different solubility enhancers, in a 1.2 pH buffer solution are shown in Table 1. The lower solubility in SLS (anionic) may be due to a lesser extent of micellization with respect to Tween 20 and Cremophor EL (nonionic surfactants), although the differences were not statistically significant. The greatest solubility enhancement was with transcutol. This result agrees with the prevailing effect of the albendazole on the intestinal absorption of the albendazole when mixed micelles (sodium taurocholate-oleic acid) were used (Estal et al., 1993).

Table 1
Albendazole solubility (mg/ml) in 5% solutions of different solubility enhancers at 1.2 pH

Lauril Na Sulfate	Tween 20	Cremophor El	Transcutol
0.514	0.722	0.612	0.778

The Fig. 2 shows the albendazole solubility in buffer solutions at different pHs as a function of percentage of transcutol.

At 1.2 pH the solubility of albendazole over a range of transcutol concentrations from 0–100% demonstrated a sigmoid solubility profile.

The influence of transcutol on the albendazole solubility increases as the pH of the buffer solution is increased. The enhancement can be fitted to an exponential plot (Orienti et al., 1994):

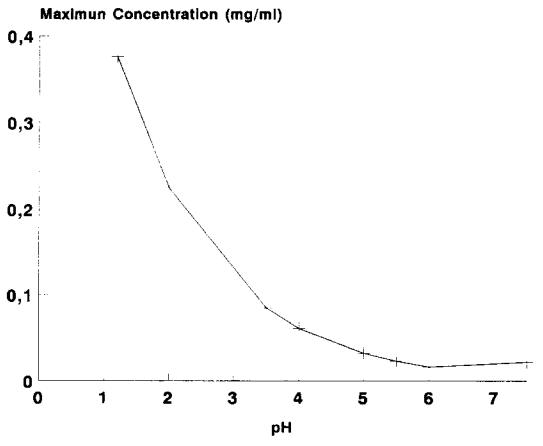

Fig. 1. Solubility (mg/ml) of albendazole in various pH buffer solutions.

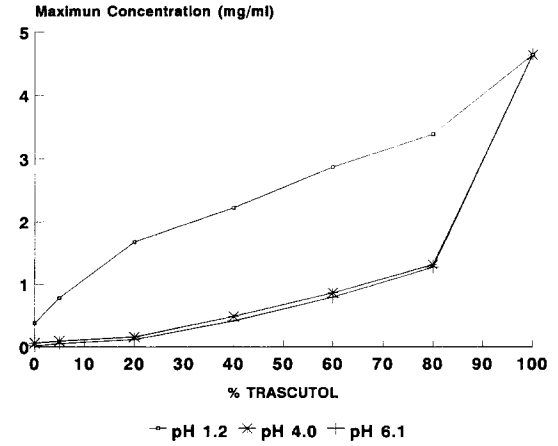

Fig. 2. Solubility (mg/ml) of albendazole in a pH 1.2 buffer solution plotted at different percentages of Transcutol.

Table 2
Fitting of albendazole solubility data (mg/ml) from Fig. 2 to an exponential plot of different percentages of Transcutol

Buffer solutions	%Transcutol	r^2	Intercept (K)	Exponent (n)
pH 1.2	5–80%	0.9976	338	0.52
pH 4.0	20–80%	0.9989	1.71	1.52
pH 6.0	20–80%	0.9989	0.70	1.72

$$X = KS^n$$

Where, X represents the transcutol percentage, S the albendazole solubility, K the acceleration period and n, the influence of the solubility cosolvent used (transcutol) on the drug solubility (albendazole).

So, for the cosolvent systems including buffer solutions of pH 4.0 and 6.0 at percentages between 0–20% of transcutol, there is an initial acceleration phase which befits the lag phase (Table 2).

This acceleration phase is almost non-existent in the solvent systems prepared with a 1.2 pH buffer solution. At this 1.2 pH buffer system the value of the lag phase is 0.338 mg/ml. This value is similar to the one obtained with the 1.2 pH buffer solution without any solubility enhancer (0.376 mg/ml). When the transcutol percentage was between 20–80%, the solubility increases exponentially as the transcutol percentage is increased.

The exponent n values are higher as the pH is increased (Table 2). thus while at 1.2 pH the n value is 0.52, (which is quite similar to a Higuchi Square Root Kinetic law), the values of n at pH 4.0 and 6.0 are 1.52 and 1.72 respectively. This indicates a greater influence of the cosolvent with increasing pH.

The albendazole solubility is higher in the 1.2 pH buffer solution, but this pH is inconvenient for oral administration. Also, it is likely that, as the pH in the gastro-intestinal medium is higher than 1.2, albendazole will precipitate out, with little chance of resolubilization. By microscopic evaluation it is observed that the solvent systems at pH 1.2 with 20% or higher transcutol concentration clear solutions, but as the pH is increased a precipitation phenomenon occurs, with the appear once of small and spherical crystals. This may be due to the ability of the transcutol to increase the wettability of the precipitated drug. These results are similar to those obtained by Sheen et al. (1995) with transcutol and other poorly soluble drugs.

This increase in the wettability of the precipitated drug, taken against the toxicity of transcutol (DL_{50} of transcutol administered orally is 8.69 g/kg in rat) (Merck Index, 1989) led us to select a 40% of transcutol in 1.2 pH buffer as the most suitable solvent system for albendazole.

3.1. Stability

The degradation of albendazole in a buffer solution (pH 1.2) containing 40% transcutol at temperatures of 4, 25, 45 and 70°C indicated a first-order process (Fig. 3). The plot is concave downwards, indicating that the reaction is accelerating with time. Similar acceleration plots, or sigmoid decomposition plots with initial accelera-

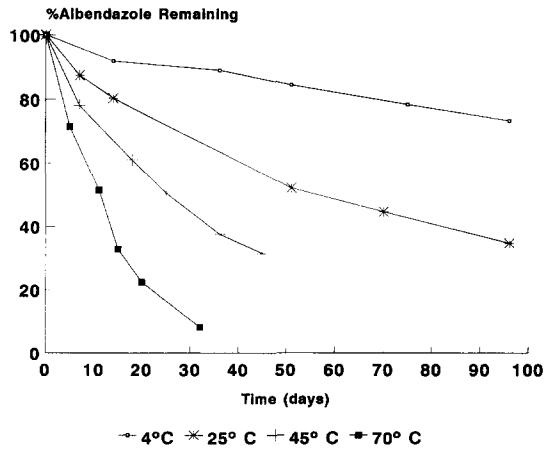

Fig. 3. Stability profiles of albendazole in a buffer solution (pH 1.2) containing a 40% of Transcutol at temperatures of 4, 25, 45 and 70°C.

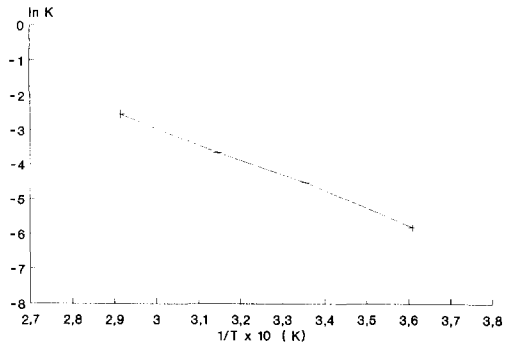

Fig. 4. Arrhenius plots of the rate constant for the albendazole in a buffer solution (pH 1.2) containing a 40% of Transcutol.

tion phases, have been reported previously for other compounds. The acceleration phase of sigmoid decomposition curves may be approximated by the equation (Snavely et al., 1993):

$$X = Kt^n$$

Where X is the percent decomposed, t is time and k and n were constants.

When adjusted to a logarithmic equation, the curves are biphasic (Fig. 4) with an initial lag phase and terminal linear portions. These results allow us to fit the degradation of the albendazole solution to a pseudo-first order plot. The effect of temperature on the hydrolysis rate of albendazole has been investigated to gain insight into the mechanism. The hydrolysis rate constants were dependent on the temperature of storage.

Fig. 4 contains Arrhenius plots of the solution at different temperatures. The plots showed good linearity with a correlation coefficient of 0.9989.

$$\ln K = 11.05 - 4663.09\, 1/T\ (°K)$$

It was found that the half-lives ($t_{1/2}$) and t_{90} for a buffer solution (pH 1.2), containing a 40% solution of Transcutol at a temperature of 4°C were longer than those obtained after a storage at a temperature of 25°C. Thus at 4°C, the buffer solution (pH 1.2) containing a 40% Transcutol solution gave a half-life of 224 days and a t_{90} of 34 days. However, at 25°C, the buffer solution (pH 1.2), containing 40% Transcutol gave a half-life of 69 days and a t_{90} of 10 days, indicating that albendazole solution is significantly more stable at 4°C.

We can thus conclude that this study may be used as a model in the development of a very poor water soluble drug in liquid formulation.

The albendazole solubility was increased by the use of a buffer solution (pH 1.2), containing Transcutol. The optimum concentration of Transcutol in the buffer solution (pH 1.2) was determinated to be 40% based on the solubility data. The albendazole solution is significantly more stable at 4°C.

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