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Buffer capacity and precipitation control of pH solubilized phenytoin formulations

F.A. Alvarez-Núñez, S.H. Yalkowsky *

College of Pharmacy, The University of Arizona, Tucson, AZ 85721, USA

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Abstract

The main objective of this investigation is to develop a phenytoin (DPH) intravenous formulation that does not precipitate upon dilution. The effect of the buffer capacity at pH 12 of several DPH formulations on the extent and lag-time of DPH precipitation upon dilution with Sorensen's phosphate buffer (SPB) is evaluated. DPH precipitation was evaluated by means of static and dynamic in vitro dilution methods. It is shown that an increase in the formulation buffer capacity decreases substantially the extent of DPH precipitation and increases the lag-time for precipitation. In addition, a comparison between static and dynamic in vitro methods to measure precipitation is presented. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Phenytoin; In vitro precipitation; Buffer capacity

1. Introduction

Phenytoin (DPH) has been prescribed in the treatment of epilepsy and cardiac arrhythmia since 1938 (Carmichael et al., 1980). DPH is a weak acid with a pK_a of 8.3 and water solubility of 20.3 μg/ml (Agarwal and Blake, 1968; Schwartz, et al., 1977). In order to obtain the desired concentration of 50 mg/ml in the IV commercial formulation (Elkins-Sinn) the pH is adjusted to 12, and 40% propylene glycol (PG) and 10% ethanol (EtOH) are added.

Since the solubility of DPH is dependent upon dissociation, in vivo and in vitro precipitation of the free acid can occur as a result of the pH changes that accompany dilution. In fact, the literature is replete with reports of crystallization occurring when DPH sodium solutions are mixed with blood or various intravenous admixture fluids (Schroeder and De Luca, 1974; Pfeifle et al., 1981; Surakitbanharn et al., 1994). Precipitation at the intravenous administration site and/or the

* Corresponding author. Tel.: +1-520-626-1289; fax: +1-520-626-4063.

E-mail address: yalkowsky@pharmacy.arizona.edu (S.H. Yalkowsky)

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presence of crystals in the dosage form has been related to irritation and phlebitis. This is manifested most often as pain, burning, or itching at the injection site, although severe sequelae such as necrosis have been reported (Wilensky and Lowden, 1973; Tuttle, 1977; Kilarski et al., 1984; Jamerson et al., 1994).

Schroeder and De Luca (1974) measured the amount of DPH crystals produced by the mixing of DPH formulation with human plasma. These authors observed that both the amount and size of the DPH crystals increase with a decrease in the plasma to DPH formulation ratio. Markowsky et al. (1991) reported the pH and concentration changes at different times of several brand name DPH formulations upon dilution with a fixed amount of normal saline. Their study shows that while most mixtures precipitated, Dilatin® brand does not form crystals for up to 2 h after dilution with normal saline. The absence of precipitation for this brand was related to its significantly higher admixture pH when is compared with the other brands.

Surakitbanharn et al. (1994) reported that the presence and the amount of DPH precipitate depend upon the initial pH of the formulation and the pH and buffer concentration of the dilution media. They developed an equation to calculate the change in solubility resulting from the change in pH due to dilution. Their study used a static method with Sorensen's phosphate buffer (SPB) as dilution media. In addition, their study shows that supersaturated solutions of DPH may or may not actually precipitate in a given period of time.

The lag-time or induction time for precipitation is defined as the time elapsing between the creation of the supersaturation and the formation of a detectable quantity of the precipitate (Boistelle and Astier, 1988). If a supersaturated solution is created when a formulation is diluted, a long induction time for precipitation is due to the retarded nucleation and crystal growth (Kibe et al., 1985).

The main objective of this investigation is to develop a safer DPH intravenous formulation. The effect of the buffer capacity at pH 12 of several DPH formulations on the extent and lag-time of DPH precipitation upon dilution with pH 7.4 SPB will be evaluated. In addition, a comparison between static and dynamic methods to measure precipitation will be presented.

2. Materials and methods

2.1. Materials

DPH sodium, potassium phosphates, and PG were used as provided by Sigma, St. Louis, MO. Ethanol (200 proof dehydrated alcohol, USP Punctilious, Quantum) was used as received. The water used was filtered through a double-deionized purification system (Milli-Q Water System from Millipore). The SPB was prepared according to Diemm and Lentner (1974). The buffer capacity (β) at pH 12.0 of each formulation was adjusted with potassium phosphate buffer. In the case of the formulation at $\beta = 0.02$ the pH was adjusted with KOH.

2.2. Methods

2.2.1. Static precipitation method and evaluation of precipitation lag-time

One ml of DPH formulation was added to a test tube containing 1 ml of SPB. The mixture was agitated for approximately 3 s. The presence or absence of DPH crystals was visually determined. One ml of this mixture was added to 1 ml of SPB, and the agitation and evaluation of precipitation were repeated. This serial dilution process was repeated ten times. Two individuals independently evaluated all samples. In a separate experiment the pH of similar samples was evaluated immediately after the agitation step.

The lag-time for precipitation of similar samples was obtained by the above experimental procedure, but in this case the visual determination of the DPH crystals was performed at several times (i.e. 0, 10, 30, 60 and 900 min) after each dilution.

2.2.2. Dynamic precipitation method

The experimental set up is described elsewhere in detail (Yalkowsky et al., 1983). Briefly, the dilution media (SBP) was pumped through Tygon tubing (1/32 inch I.D.) by a peristaltic pump at

the rate of 40 ml/min. The tested formulation was injected at three rates (0.5, 1.0, and 1.5 ml/min) into dilution media with the aid of a syringe pump. The absorbance of the dilution media-formulation mixture was evaluated by means of a spectrophotometer equipped with a flow cell. The mixing distance (i.e. the distance between the injection site and the flow cell) was 54 cm. The increase in turbidity at 500 nm was assumed to be a measure of precipitation.

3. Results and discussion

Fig. 1 shows the pH change of unbuffered and buffered pH 12 placebo formulations as a function of dilution fraction (DF). Note that the pH of the unbuffered formulation drops to practically pH 7.4 at the first dilution (DF = 0.5), whereas the buffered formulations do not reach this pH until the fifth dilution (DF = 0.03).

Fig. 2 shows the pH-DF profiles of unbuffered ($\beta = 0.02$) and buffered pH 12 DPH formulations. Again the pH decrease with diluting is greatest for the unbuffered formulation. The presence or absence of precipitation is indicated by closed and open symbols, respectively. The unbuffered formulation precipitates at the first dilution (DF = 0.50), while the formulation at $\beta = 0.16$ does not precipitate until the fifth dilution, and the $\beta = 0.27$ buffered formulation does not precipitate at any dilution.

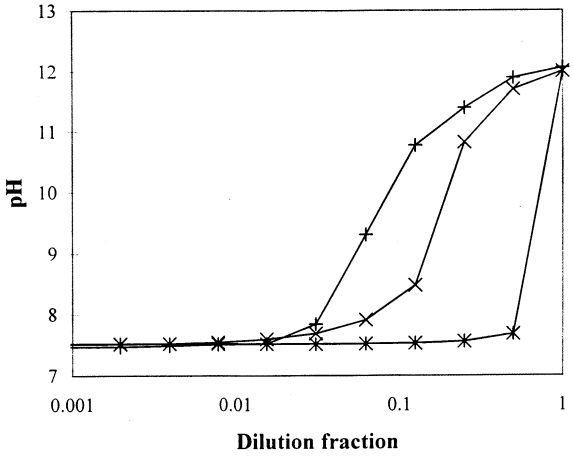

Fig. 1. pH as a function of dilution fraction of phenytoin (DPH) placebo formulations at different buffer capacities (*, ×, and +, buffer capacity 0.00, 0.16, and 0.22).

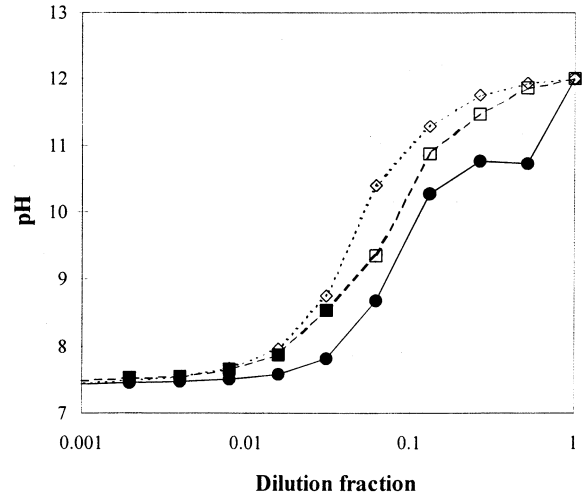

Fig. 2. pH as a function of dilution fraction of phenytoin (DPH) formulations at different buffer capacities (●, ■, ◆, buffer capacity 0.00, 0.16, and 0.27, respectively). Closed and open symbols indicate the presence or absence of precipitation, respectively.

Since the driving force for precipitation is supersaturation, the precipitation of DPH formulations as a function of dilution can be explained in terms of the difference between concentration, which is dependent of DF, and solubility, which is dependent on pH. Note that in the case of a weak electrolyte, such as DPH, supersaturation at a given DF is a function of pH. All formulations are initially (i.e. DF = 1) clear solutions at pH 12. Fig. 2 shows that at a DF of 0.5 the unbuffered formulation has a much lower pH than the buffered formulations. At this pH the solubility of DPH is lower than its concentration. In fact, this formulation is sufficiently supersaturated to precipitate instantaneously. On the other hand the pH of the buffered formulations is not low enough to produce supersaturation and there is no precipitation. The figure also shows that the $\beta = 0.27$ buffered formulation resist precipitation to a greater extent than the $\beta = 0.16$ formulation.

Interestingly, the unbuffered formulation is less sensitive than the buffered formulations to pH changes at DF between 0.500 and 0.125. Al-

though it is not shown the plateau was observed for several buffered formulations. The resistance of the unbuffered formulation to pH change is believed to be due to the precipitation of DPH free acid. In the non-precipitating pH 12 phosphate buffered placebo solution shown in Fig. 1 the change in hydrogen ion concentration is mainly compensated by the shift of the buffer reaction $H^+ + PO_4^{-3} \rightarrow HPO_4^{-2}$. However, in the precipitating DPH formulations the precipitation reaction ($DPH^- + H^+ \rightarrow DPH\downarrow$) competes with the buffer reaction for the hydrogen ions. That is, while DPH precipitation is occurring, fewer hydrogen ions are available to shift the buffering reaction and therefore the concentration of hydronium ions (and thus the pH) is relatively constant.

Table 1 shows the presence or absence (+ or −, respectively) of precipitation at different times as a function of DF for the formulation at $\beta = 0.16$. It is shown that there is no precipitation at DF of 0.5 up to 15 h (900 min) after mixing. Also, this table shows that the lag-times for precipitation at DFs 0.25 and 0.125 are 900 and 30 min, respectively, and that precipitation is instantaneous at all DFs lower than 0.063.

Since an increase in buffer capacity decreases the supersaturation or driving force for precipitation, longer times for precipitation are expected at higher buffer capacities. This is seen in Fig. 3 which shows the relationship between the lag-time for precipitation and the formulation buffer capacity. It is clear that an increase in the formulation buffer capacity increases the time required for the formation of DPH crystals. Thus, the increase in β is not only controlling the pH of the DPH formulations upon dilution, but it is also increasing the lag-time for DPH crystal formation. This finding is quite relevant because if the lag-time for precipitation of a supersaturated solution is longer than the transit time between the injection site and the site of infinite dilution, the solution will not precipitate.

Table 1
Presence (+) or absence (−) of precipitation at different times as a function of dilution fraction for phenytoin (DPH) formulation at $\beta = 0.16$

Dilution fraction	Time (min)				
	0	10	30	60	900
1.000	−	−	−	−	−
0.500	−	−	−	−	−
0.250	−	−	−	−	+
0.125	−	−	+	+	+
0.063	+	+	+	+	+
0.031	+	+	+	+	+
0.016	+	+	+	+	+
0.008	+	+	+	+	+
0.004	+	+	+	+	+

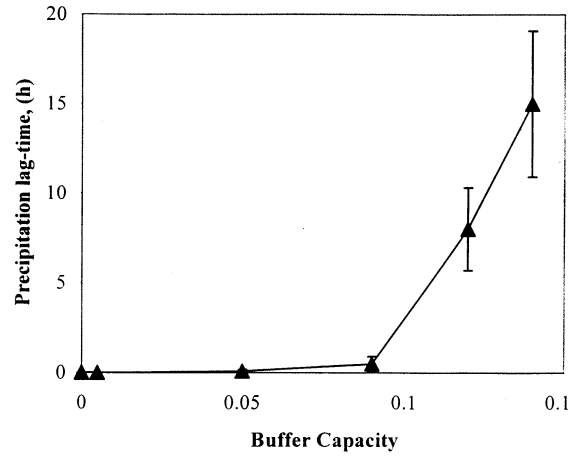

Fig. 3. Lag-time for precipitation at dilution fraction (DF) = 0.25 of phenytoin (DPH) formulations as a function of buffer capacity.

Fig. 4 shows the results of the dynamic injection of pH 12 DPH formulations at $\beta = 0.02$, $\beta = 0.16$, and $\beta = 0.27$ at three injection rates into a 40 ml/min stream of SPB. The latter is assumed to be a reasonable model for blood. In all cases the higher the β the lower the area under the curve (AUC) at the same injection rate. Actually, the formulation at highest buffer capacity has practically no precipitation at any of the injection rates. Fig. 4 shows that the AUC of either formulation increases when the formulation injection rate increases. This observation is due to the higher degree of DPH supersaturation. Although the presence of precipitate in these studies is consistent with the results from the static method, the dynamic method enables the demonstration of the fact that the extent of precipitation is sensitive to the degree of DPH supersaturation.

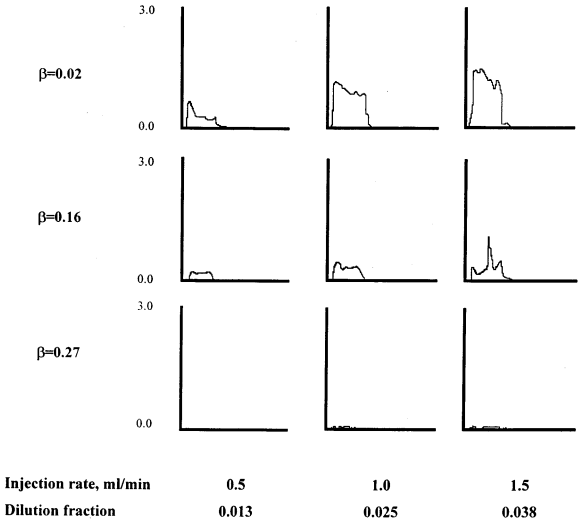

Fig. 4. Absorbance at 500 nm as a function of time at three buffer capacities (β) and three formulation injection rates of phenytoin (DPH) formulations.

4. Conclusions

An increase in the formulation buffer capacity decreases the extent of DPH precipitation and increases the lag-time for the precipitation. Also, the experimentally simpler static and the more realistic dynamic methods show comparable results in evaluating DPH precipitation. These evaluation techniques confirm that a DPH formulation with a buffer capacity of 0.27 will not precipitate when diluted with SPB. It is believed that such a formulation will not precipitate upon IV injection.

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