Original Article

Physicochemical and Microbiological Stability of Phenytoin Sodium Extemporaneous Suspension

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ABSTRACT

Objective: To study the physicochemical and microbiological stability of phenytoin sodium extemporaneous suspension. **Methods**: The extemporaneous suspension was prepared from the prompt release capsules of phenytoin sodium (100 mg/capsule). Four capsules were uncapped and the granules were ground into fine powders using a mortar and pestle. The powders were dispersed in sugar-free suspension structured vehicle to achieve the concentration of 10 mg/mL. The suspensions were stored in glass and polyethylene plastic bottles and kept at 4, 25, and 40 ºC. The percent initial drug remaining, pH, sedimentation volume, viscosity, X-ray-powder diffractometry and microbial stability were evaluated. **Results**: The percent phenytoin sodium concentration remained above 90% of initial concentration up to 56 days at all temperatures. The pH of suspensions were rather constant in both glass and polyethylene containers. The sedimentation volumes were 0.39 - 0.41 and redispersibilities were 3.3 - 3.5 throughout the study. The rheology of prepared suspension exhibited a shear-thining system. The X-ray powder diffractogram showed that sediment of phenytoin sodium in sugar-free suspension structured vehicle was in free acid form and no change in polymorphic form was observed after storage at 25 ºC for 56 days. **Conclusion**: The extemporaneous suspension was chemically stable up to 56 days at 4, 25, and 40 ºC. The prepared suspension met USP specification in microbial examination of nonsterile product after storage at 25 ºC for 56 days.

Keywords: extemporaneous, phenytoin, stability

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Introduction

Phenytoin is an effective anticonvulsant drug which was used mainly in the prophylactic management of tonic-clonic seizues and partial seizues with complex symtomatology. It is also used for the prevention and treatment of seizures occurring during surgery.[1] The usual initial oral dosage of phenytoin for treatment of seizures in children is 5 mg/kg or 250 mg/m^2 daily administered in 2 or 3 equally divided doses. Total dosage should not exceed 300 mg daily and maintenance dosage for treatment is required.[2] Furthermore, phenytoin can be used in neonates, infants and children with seizures. In the U.S. market, phenytoin is available in various dosage forms such as prompt release tablets and capsules, extended release capsules, injection and suspensions. However, the oral suspensions of phenytoin are not commercially available in many countries which constitute a small market such as some countries in Europe and Thailand. Therefore it is necessary to prepare an oral liquid dosage form from prompt releases tablets or capsules by dispersing or dissolving in a suitable vehicle. These are referred to as extemporaneously prepared formations.[3]

Because most drugs are not completely soluble, suspensions are generally extemporaneously prepared. The

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extemporaneous oral liquid suspensions should be easily prepared, allow dosage flexibility and ensure palatability. The commercially available suspending vehicles, eg. Ora-Sweet®, Ora-Sweet SF®, Ora-plus®, Ora-Blend® and SyrSpend SF®, are widely used to prepare extemporaneous suspensions. However, since these vehicles are occasionally not stocked in a hospital, hospital pharmacists must prepare a vehicle for extemporaneous preparation. The combination of viscosity enhancing agent, sweetening agent and preservative is used to prepare a vehicle providing a good physical, chemical and microbiological stability. Carboxymethylcellulose methylcellulose and xanthan gum are generally used as suspending agent due to its desirable rheological behavior.[4]

In practice, the documented stability data are used to determine the beyond-use date of extemporaneous preparation.[5] However, a major problem of many extemporaneous preparations is due to a lack of information regarding suitability and stability.[6] If the stability information is not available, the USP suggested the beyond-use date of 14 days if stored in a refrigerator.[7] Since there was a lack of stability information of phenytoin extemporaneous preparation, a study of the stability of such preparation is required. Additionally, phenytoin is usually dispensed to patients continuously for maintenance therapy. If extemporaneous phenytoin preparation is stable longer than 14 days, less frequent dispensing is required. The patient will benefit from more convenience and reduced medication error.

The purpose of this study was to determine the physicochemical stability and microbial stability of an extemporaneous phenytoin suspension when stored at 4, 25 and 40 ºC. In this study, the sugar-free suspension structured vehicle, recommended in USP 26/NF 21, was used to disperse drug granules due to simple preparation technique needed and good palatability offerred.[8] The percent initial drug remaining, pH, sedimentation volume, viscosity, powder diffraction patterns, and microbial stability were evaluated.

Materials and Methods

Chemicals and reagents

Capsules containing 100 mg of pheytoin sodium (commercial available in Thailand) were used. Xanthan gum and hydrocortisone were obtained from Sigma (USA). Sorbitol and mannitol were purchased from Ajax Finechem (New Zealand). Potassium sorbate and citric acid anhydrous were supplied by Fluka (USA). Glycerin and saccharin sodium were provided from P.C. Drug Center Co, Ltd, Thailand. Potasium dihydrogen phosphate was from Carlo Erba, Italy. Methanol was of HPLC grade (Labscan, Thailand). Other reagents were analytical grade and purchased from Merck, Germany.

Extemporaneous preparation

The sugar-free suspension structured vehicle was prepared according to the USP 26/NF 21. The vehicle consists of 0.20% xanthan gum, 0.20% saccharin sodium, 0.15% potassium sorbate, 0.10% citric acid, 2.0% sorbitol, 2.0% mannitol, 2% glycerin and purified water qs. to 100 mL. The extemporaneous oral suspension was prepared using prompt release capsules containing 100 mg of phenytoin sodium. Four capsules were uncapped and the granules were ground into fine powder in a mortar. The fine powder was dispersed in a sugar-free suspension structured vehicle to achieve a concentration of 10 mg/mL. The suspensions were stored in glass and polyethylene plastic bottles and kept at 4, 25, and 40 ºC. All samples were protected from light.

Physicochemical stability test

Analytical method

The content of phenytoin sodium was determined with a modification of previous reports.[9,10] A liquid chromatograph system (Perkin Elmer Instruments, USA) equipped with a C-18 HPLC column (Hypersil 25 cm x 4.6 cm, Thermoscientific, England) was used. The mobile phase consisted of MeOH : 50 mM phosphate buffer (55:45) adjusted with 2 M phosphoric acid to pH 4 at a flow rate of 1 ml/min. The UV-VIS detector was operated at 235 nm. Hydrocortisone was used as an internal standard. The relationship of peak area ratio between phenytoin sodium at concentrations of 40, 80,

120, 160 and 200 μg/mL and hydrocortisone at concentration of 32 μg/mL was plotted as a standard curve. The method validation was determined for specificity, precision, accuracy, linearity, limit of detection (LOD) and limit of quantification (LOQ).

Drug analysis

The extemporaneous suspensions were sampled on days 0, 7, 14, 21, 28 and 56. After gentle shaking, 1 ml of the extemporaneous suspension was pipetted into a 100-mL volumetric flask. The solution of hydrocortisone solution (1 mg/mL, 3.2 mL) was added, followed by addition of mobile phase up to 100 mL. The mixture was sonicated about 10 min and filtered through a 0.45 μm nylon membrane filter. Twenty μL of this filtered sample was injected onto HPLC column. All samples for each storage condition were assayed in four replicates. The initial concentration (day 0) of phenytoin sodium was designated as 100%. The phenytoin sodium concentration at each time point was expressed as a percentage of the initial concentration. A sample was considered stable if percentage of phenytoin sodium was above 90% of the initial concentration.[11,12]

pH measurement

The pH of extemporaneously prepared suspension was measured using pH meter (Orion®, USA) on days 0, 7, 14, 21, 28 and 56. The pH 4.0 and pH 7.0 standard buffer solutions (Thermo Electron Corporation, USA) were used to calibrate the pH meter.

Sedimentation volume

The extemporaneous suspensions were kept in a 100-ml graduated cylinder at 25 ºC after preparation. The sediment of suspensions was measured on days 7, 14, 21, 28 and 56. The sedimentation volume was calculated as $F = V_u/V_o$; where F = sedimentation volume, and V_u and V_o = volume of sediment (mL) and volume of suspension (mL), respectively.[13]

Redispersibility

The redispersibility was determined with a slight modification from the method of Bhargava and colleagues.[13] The extemporaneous suspension in a 100-ml glass cylinder was rotated through 135º and turned back at the same position. The end point was taken when the base of the graduated cylinder was free from sediment. The number of rotation was recorded.

Viscosity

The extemporaneous suspension was kept at 25 ºC and the viscosity was determined on days 0, 28 and 56. The viscosity was measured using Brookfield Viscometer (Model DV-II+, Brookfield Engineering Lab, Inc, USA) using LV spindle No.1 at speeds of 20, 50, and 100 rpm.

X-ray powder diffraction (XRD)

Phenytoin sodium was weighed and dispersed in a sugar-free suspension structured vehicle to yield a concentration of 10 mg/mL. The suspension was kept at 25 ºC and analyzed on days 0 and 56. The suspension was centrifuged at 10,000 rpm for 2 hours using a high speed centrifugation (Tomy, Japan). The supernatant was discarded and the sediment was kept in an oven (Mammert, Germany) at 40 ºC for about 2 days until dried. The sample was ground using an agate mortar and pestle then placed in a cavity of the sample holder of X-ray diffractometer. X-ray diffraction patterns of samples were obtained using X-ray diffractometer (JEOL, Japan) over a range of 5-60º, 2θ angle, with a step angle of 0.02. The X-ray powder diffraction patterns of phenytoin and phenytoin sodium powder were also recorded to compare with that of the sediment.

Microbial stability test

Microbial test of extemporaneous suspension stored at 25 ºC was performed on days 28 and 56, according to monograph microbiological examination of nonsterile products.[14] The extemporaneous suspension was diluted with Casein-Peptone Lecithin Polysorbate Broth (PLPB) in a dilution of 1:10. A portion of diluted suspension was then streaked on the Tryptic Soy Agar (TSA) plate for bacteria determination. The petri-dish was incubated at 30 – 35 ºC for 3 - 5 days to observe bacteria. For yeast and mould determination, the extemporaneous suspension was diluted with PLPB in a dilution of 1:10, then streaked on the Sabouraud-Dextrose Agar (SDA) plate. The petri-dish was incubated at temperature 20 – 25 ºC for 5 - 7 days to

observe yeasts and moulds. For determination of *Escherichia coli (E. coli)*, the extemporaneous suspension was also diluted with PLPB in a dilution of 1:10. Ten mL of diluted suspension was used to inoculate in 100 mL Tryptic Soy Broth (TSB), mixed, and incubated at 35 – 37 ºC for 18 - 48 hours. One mL of inoculated TSB was transferred to 100 mL of MacConkey Broth (MCB), incubated at 43 – 45 ºC for 18 - 24 hours. Then, the broth was subcultured on a plate of MacConkey Agar (MCA) at 35 – 37 ºC for 18 - 72 hours. The growth of colonies indicates the possible presence of *E. coli*.

The microbial count was considered to be the average number of colony-forming units (cfu) found in agar. The experiment was performed in duplicate. Based on USP31/NF26, the microbial quality of non-sterile dosage forms for oral use meets requirements with a total aerobic microbial counts of less than 200 cfu/ml, a total combined yeasts/moulds of less than 20 cfu/ml and the absence of *E.coli*.[14]

Results and Discussion

Physicochemical Stability

Drug Analysis

The HPLC technique was suitable for determination of phenytoin sodium. Under the condition used, the retention time of phenytoin sodium and hydrocortisone were 7.6 - 7.8 min and 9.4 - 9.5 min, respectively. The excipients in sugar-free suspension structured vehicle were also separated. The peaks at 2.7 - 2.8 min and 5.6 - 5.9 min were attributed to saccharin sodium and potassium sorbate, respectively (Figure 1). The standard curve was linear and the coefficient of determination for the standard curve (r^2) was 0.9989 - 0.9999 for the entire study. The intra-day and inter-day coefficients of variation were less than 2% at each concentration of three replicates. The limit of detection was 0.5 μg/mL (signal to noise ratio of 3:1) while limit of quantification was 2 μg/mL (signal to noise ratio of 10:1). The validation data indicated that our method was appropriate for analytical assay.[15] The analytical results showed that the percent phenytoin sodium concentration remained above 90% of the initial concentration after storage for 56 days at 4, 25 and 40 ºC in both glass and polyethylene plastic containers. The percent of initial concentrations were in a range of 94.39 - 104.15% as shown in Figures 2 and 3. The previous study reported that the loss of phenytoin during nasogastric administration was attributed to a binding interaction between phenytoin and plastic tubing.[16] However, our data showed that the loss of phenytoin was not observed in polyethylene plastic. Furthermore, the percent remaining of phenytoin sodium was more than 90% at 40 ºC throughout 56 days indicating that phenytoin sodium was stable at high temp erature. This is consistent with previous report that phenytoin is very stable even under conditions of extreme stress. After refluxing phenytoin in 2.5 N HCl for seven hours, essentially complete recovery of phenytoin was obtained.[17]

pH measurement

It was found that pH of sugar-free suspension structured vehicle was about 4.1 - 4.2. The 10 mg/mL phenytoin sodium extemporaneous prepared suspension was a white and readily redispersible suspension. The pH of phenytoin sodium suspension increased to 10.58 - 10.66 after freshly

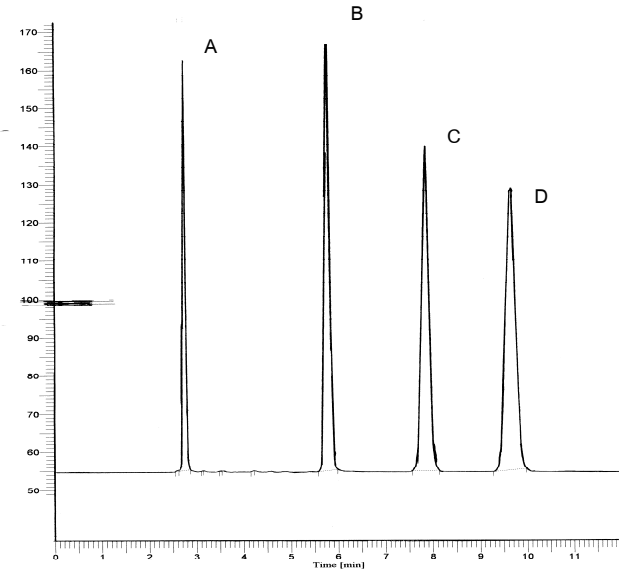

Figure 1 HPLC chromatogram of phenytoin sodium extemporaneous suspension representing saccharin sodium (peak A), potassium sorbate (peak B), phenytoin sodium (peak C) and hydrocortisone (peak D).

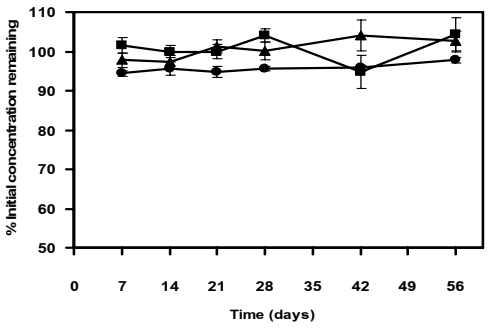

Figure 2 Percentage of initial concentration of 10 mg/mL phenytoin sodium extemporaneous preparation (mean ± SD, n = 4) after storage in glass container at 4 °C (●), 25 °C (■) and 40 °C (▲) on days 7, 14, 21, 28, 42 and 56.

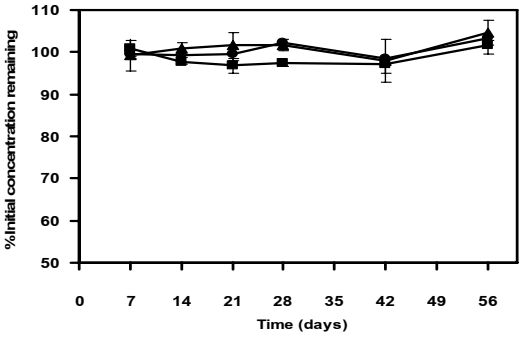

Figure 3 Percentage of initial concentration of 10 mg/mL phenytoin sodium extemporaneous preparation (mean ± SD, n = 4) after storage in polyethylene plastic container at 4 °C (●), 25 °C (■) and 40 °C (▲) on days 7, 14, 21, 28, 42 and 56.

Table 1 pH of phenytoin sodium extemporaneous suspensions in glass and polyethylene plastic container at 4, 25 and 40 ºC (mean ± SD, n = 4).

Day	pH					
	Glass container			Plastic container		
	Temp 4 ºC	Temp 25 ºC	Temp 40 ºC	Temp 4 ºC	Temp 25 ºC	Temp 40 ºC
0	10.66 ± 0.01	10.62 ± 0.05	10.62 ± 0.01	10.58 ± 0.03	10.61 ± 0.04	10.63 ± 0.05
7	10.71 ± 0.01	10.64 ± 0.04	10.32 ± 0.01	10.67 ± 0.01	10.63 ± 0.04	10.34 ± 0.08
14	10.68 ± 0.02	10.60 ± 0.04	10.31 ± 0.04	10.65 ± 0.02	10.61 ± 0.04	10.33 ± 0.07
21	10.69 ± 0.02	10.55 ± 0.04	10.31 ± 0.05	10.63 ± 0.01	10.53 ± 0.05	10.33 ± 0.07
28	10.62 ± 0.01	10.47 ± 0.05	10.26 ± 0.02	10.56 ± 0.02	10.44 ± 0.04	10.33 ± 0.08
42	10.67 ± 0.01	10.50 ± 0.06	10.35 ± 0.02	10.60 ± 0.01	10.51 ± 0.06	10.41 ± 0.07
56	10.70 ± 0.02	10.48 ± 0.07	10.38 ± 0.02	10.65 ± 0.01	10.50 ± 0.05	10.41 ± 0.08

prepared. The increase of the pH was attributed to sodium salt of the drug. The pH values were rather constant in a range of 10.26 - 10.71 after storage for 56 days (Table 1).However, the pH slightly decreased after storage at 40 ºC. The data indicated that type of container did not affect pH. Since pH of the preparation was higher than pK_a of the drug (8.3 at 25 ºC)[17], the higher pH of the system than pK_a could result in a higher proportion of ionized form which might cause bitter taste. Addition of buffer system in the vehicle to control pH of suspension to about 6 or 7 was one of the methods for masking the bitter taste of the phenytoin sodium extemporaneous suspension.

Sedimentation volume and redispersibility

The sedimentation volumes were between 0.39 and 0.41 and redispersibilities were in a range of 3.3 - 3.5 (Table 2). The sedimentation volumes and redispersibility were relatively constant at 25 ºC throughout 56 days indicating that suspension was easily redispersed to yield uniform suspension. Additionally, no caking was observed. This result indicated that the sugar-free suspension structured vehicle was a desirable vehicle for good physical stability.

Table 2 Sedimentation volume and redispersibility of phenytoin sodium extemporaneous suspensions on days 7, 14, 21, 28, 42, 56 at 25 °C (mean ± SD, n = 4).

Day	Sedimentation volume (F)	Redispersibility
7	0.41 ± 0.01	3.3 ± 0.5
14	0.40 ± 0.01	3.3 ± 0.5
21	0.40 ± 0.01	3.3 ± 0.5
28	0.40 ± 0.01	3.5 ± 0.6
42	0.40 ± 0.01	3.5 ± 0.5
56	0.39 ± 0.01	3.5 ± 0.5

Viscosity

After storage at 25 ºC for 56 days, the viscosities were not significantly different from the freshly prepared suspensions at the same speed of needle (Table 3). The viscosity decreased with increasing speed of needle indicating that the prepared suspension exhibited a shear thinning behavior. This result is in accordance with previous reports that xanthan gum exhibits plastic or pseudoplastic flow.[13,18] This behavior was possibly a result of shearing action on the long chain molecule of xanthan gum. As the shearing stress is increased, the disarranged molecules start to align their long axes in the direction of flow. This orientation reduces the resistance which further allows lowering of viscosity at increasing shearing stress.[19] Additionally, the viscosity of xanthan gum is independent of pH and temperature.[18]

Table 3 Viscosity of phenytoin sodium extemporaneous suspension on days 0, 28, 56 at 25 °C (mean ± SD, n = 4).

Day	Viscosity (cps) at various speeds		
	20 rpm	50 rpm	100 rpm
0	44.6 ± 1.1	35.0 ± 1.0	28.7 ± 1.1
28	45.6 ± 1.6	36.4 ± 0.7	29.4 ± 1.7
56	42.5 ± 3.0	34.7 ± 0.3	27.8 ± 0.4

X-ray powder diffraction

Vehicle could have influence on the habit of crystalline materials which affect physicochemical characteristics and other properties such as manufacturability, dissolution rate and absorption rate. The study of X-ray diffractogram (XRD) was to evaluate possible polymorphic modification of drug in vehicle.[20] XRD spectra of pure phenytoin sodium and phenytoin are presented in Figures 4A and 4B. According to XRD of phenytoin sodium powder, sharp peaks at diffraction angles of 2θ 8.64º, 11.40º, 13.02º, 16.60º, 17.33º, 18.52º, 20.42º, 22.48º, 26.20º and 27.86º were present. The peaks of phenytoin powder were exhibited at 8.56º, 11.30º, 12.94º, 16.56º, 17.26º, 20.34º, 22.40º, 26.12º, and 27.40º. The data suggested that both phenytoin and phenytoin sodium powder are crystalline material. The diffractogram of sediment corresponding to pure phenytoin is shown in Figure 4C. This indicated that the sediment of phenytoin sodium in sugar-free suspension structured vehicle was in free acid form. Additionally, there was no significant difference in the diffraction pattern between XRD spectra of the sediment on day 0 and day 56, indicating that no polymorphic modification occurred due to vehicle influence (Figures 4C and 4D).

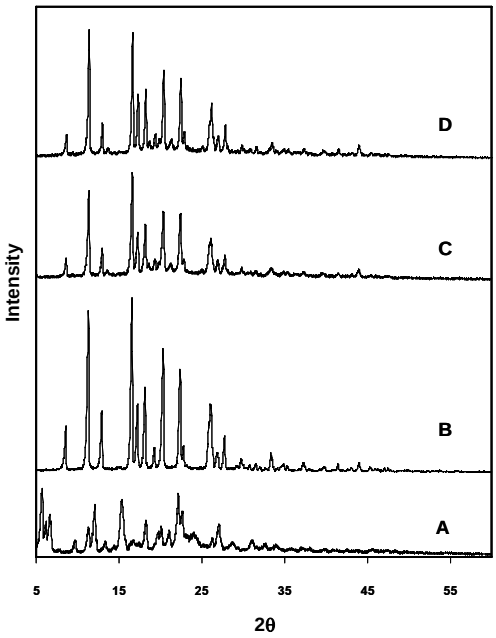

Figure 4 X-ray diffractograms of phenytoin sodium powder (A), phenytoin powder (B), sediment of phenytoin sodium on day 0 (C), and sediment of phenytoin sodium on days 56 (D).

Microbial Stability

Microbial contamination in nonsterile liquid formulations may cause foul odor, turbidity, and adversely effect palatability and appearance. High level of microorganisms may be hazardous to health especially in immunocompromised patients. By-product of microorganism metabolism may cause a change in the pH of the preparation and reduce the chemical stability.[3] The use of preservative is required to control microbial growth during the beyond-use date in extemporaneous preparations. In this study, potassium sorbate was used as a preservative in the sugar-free suspension structured vehicle. The microbial stability study showed that the fungal contaminations of 5 cfu/ml were detected on days 28 and 56. No bacteria or *E. coli* contamination was observed on both days 28 and 56. This indicated that phenytoin sodium extemporaneous suspension met the USP specifications in microbial examination of nonsterile product throughout 56 days.[14] Although our prepared suspension was in accordance with the acceptance criteria of microorganism qualification, the use of antimicrobial preservatives in formulation should be reconsidered. This is because the final pH of prepared extemporaneous suspension was higher than p*K*a of potassium sorbate (4.8) so that the ionized form of potassium sorbate was predominant.[16] Therefore, the addition of other preservatives such as parabens or the use of buffer system to control final pH of prepared suspension was suggested to ensure good microbiological stability.

Conclusions

Phenytoin sodium is stable in a sugar-free suspension structured vehicle, allowing a fairly long beyond use date. The prepared extemporaneous suspension was chemically stable up to 56 days in all temperatures (4, 25 and 40 ºC) both in glass and polyethylene containers. The pH and appearance of suspension remained constant throughout the study. The rheology of suspension exhibited a shear-thinning system. The XRD indicated that the sediment of phenytoin sodium in vehicle was in free acid form and no polymorphic change was observed throughout 56 days. Additionally, phenytoin extemporaneous suspension met the USP specifications in microbial examination of nonsterile product. However, the use of buffer system to control final pH of prepared suspension was suggested to reduce bitter taste of drug and ensure good microbial stability.

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