The Formulation Development and Stability Study of Norfloxacin Suspension

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Abstract

The norfloxacin suspension was formulated using norfloxacin powder, sodium chloride, sodium saccharin, glycerin, paraben concentrate, and purified water. It was found that the product was physically acceptable and the ingredients used in the formula did not affect the chemical stability of the drug under the studied conditions.

Keywords: norfloxacin suspension, sodium chloride, sodium saccharin, glycerin, paraben concentrate,

1. Introduction

Norfloxacin, 1-ethyl-6-fluoro-1,4-di-hydro–4–oxo–7-(1-piperazinyl)-3-quinoline car-boxylic acid, is a synthetic antibacterial fluoro-quinolone. It is effective in the treatment of urinary tract infections, gonoccocal urethritis, and infectious diarrhea [1,2]. In Thailand, the norfloxacin products are commercially available only as tablets and capsules [3]. A number of patients, especially pediatric and geriatric patients, have difficulty swallowing solid dosage forms. Therefore, a liquid dosage form of norfloxacin is needed. Since norfloxacin is a solid and is slightly soluble in water [4], a suspension dosage form is the most suitable if the product is physically and chemically stable [5,6]. In previous study [7], we found that extemporaneous norfloxacin suspensions from tablets were chemically stable but their physical characteristics depended on excipients employed in tablets used in preparation.

The purpose of this study was to formulate norfloxacin suspension using norfloxacin powder and to evaluate the physical and chemical stability of the formulation.

2. Materials and Methods

2.1 Materials

All the chemicals were purchased from suppliers in Thailand and were used without further modification. Standard norfloxacin was from Sigma (St. Louis, MO).

2.2 Formulation of norfloxacin suspension

In a preliminary study, it was found that norfloxacin powder was poorly dispersed in an aqueous medium. Therefore, glycerin was used as a dispersing agent. It was found that 4% of glycerin in the formula was suitable. Norfloxacin powder hydrated rapidly in the aqueous medium causing high viscosity, so a suspending agent was no longer needed. Due to the bitter taste of norfloxacin, sodium saccharin was used as a sweetening agent. It could increase sweetness without altering viscosity.

A 500-ml portion of norfloxacin suspension was prepared according to the formula in Table 1. Norfloxacin powder was passed through a laboratory test sieve number 50 (aperture 300 μm). It was mixed in a mortar with glycerin to form a smooth paste. A solution of sodium chloride and sodium saccharin in 350-ml portion of purified water was added to the mixture, followed by a paraben concentrate containing 10% methylparaben and 2% propylparaben in propylene glycol. After mixing, the contents of the mortar were transferred to a graduated cylinder, and purified water then was used to bring the volume to 500 ml to obtain drug strength of 20 mg/ml. The formulation was prepared in triplicate. All samples were stored in amber glass bottles at ambient temperature (28±2°C) and at 40°C to assess stability.

Table 1 Formula for the preparation of norfloxacin suspension.

Ingredients	Amount Used	
Norfloxacin powder	10.0	g
Sodium chloride	5.0	g
Sodium saccharin	2.5	g
Glycerin	20.0	ml
Paraben concentrate	5.0	ml
Purified water, qs to	500.0	ml

2.3 Study of physical properties of samples

The samples were studied for visual appearance, density, sedimentation, pH, and rheological characteristics. The viscosity values of samples were measured at various shear rates by Brookfield Rheometer Model DV-III (Brookfield Engineering Labs, MA) and then rheograms were determined.

2.4 Study of dissolution behavior of norfloxacin suspension and raw material

Suspensions may have the same problems with the deaggregation rate such as tablets and capsules do [9]. Therefore, the USP dissolution test for norfloxacin tablets [10] was modified to investigate the dissolution behavior of norfloxacin suspension and that of raw material. A pH 4.0 buffer was prepared by adding 2.86 ml of glacial acetic acid and 1.0 ml of a 50 %w/w solution of sodium hydroxide to 900 ml of water in a 1000-ml volumetric flask and diluting with water to volume. If necessary, glacial acetic acid or sodium hydroxide solution was used for adjusting to a pH of 4.0. The 750-ml of pH 4.0 buffer was used as a medium in each vessel. The test was performed using stirring paddles at the speed of 50 rpm. Suspension samples equivalent to 100 mg of norfloxacin and the 100 mg of norfloxacin raw material were transferred to the vessels, then the dissolution was carried out. The dissolution media were sampled with replacing fresh media at time intervals of 5, 10, 15, 30, 45, and 60 minutes, respectively. The dissolved amount was spectrophotometrically determined at 278 nm in comparison to a standard curve of standard norfloxacin.

2.5 Analysis of samples

Each suspension was shaken thoroughly by hand immediately before determination. A 0.5-g sample was withdrawn and dissolved with methanol to a volume of 50 ml. Of this solution, 0.3 ml was then withdrawn and diluted with pH 3 buffer to a volume of 25 ml, giving a 2.45 μg/ml concentration of norfloxacin. Each sample was assayed in duplicate by high-performance liquid chromatography (HPLC). The HPLC assay was modified from the method of Nangia et al [11]. The instrumentation included a Jasco PU 980 pump controller, Jasco 975 UV light detector with the wavelength set at 275 nm, and Jasco 807-IT integrator (Jasco, Japan). A C_{18} column (Microbondapak by Waters, USA, 30 cm x 3.9 mm) was the stationary phase. A mobile phase of water-acetonitrile (80:20 %v/v) containing 10 mM of monobasic potassium phosphate, 10 mM of sodium lauryl sulfate (SLS), and 20 mM of tetrabutylammonium sulfate (TBS) adjusted to pH 3 was used. The injection volume was 50 μl. A flow rate of 1.25 ml/minute was employed. The peak area was used for calculating the quantity.

3. Results and Discussion

Each sample of the norfloxacin suspension had good visual appearance with white color and high sedimentation volume. The high sedimentation volume showed that the drug particles formed flocs. It was sweet initially, followed by a bitter aftertaste. Its density was 0.980±0.013 g/ml (mean±SD, n=3). The initial pH was 7.43±0.04 (mean±SD, n=6). No appreciable change in visual appearance and pH was observed in any samples. Norfloxacin showed a zwitterionic form at the pH between 6 and 10 [1]. Therefore, the solubility of drug in this formula was low and consistent.

3.1 Rheological properties

Rheograms of samples presented in Figure 1 showed the plastic flow with thixotropic property due to the flocculation of drug particles in the suspension [8]. It was found that repeated viscosity measurement made the decrement of viscosity. This may be because the structural network of flocs was destroyed in the previous measurement while structural reformation was not yet completed. Although the samples had high viscosity at rest, they could be poured after a reasonable amount of shaking.

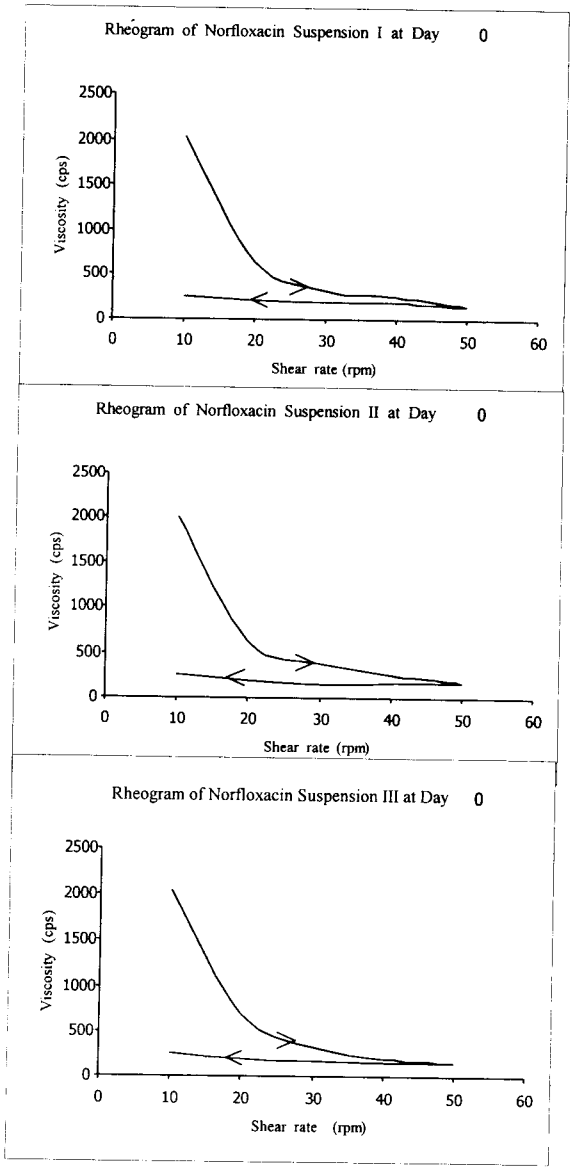

Figure 1 Rheograms of norfloxacin suspension prepared in triplicate.

3.2 Dissolution behavior

The percentages of drug dissolved from suspension were different from (seemed to be lower than) those from the raw material alone as shown in Table 2. This might be because the drug particles in the suspension were flocculated.

Table 2 Dissolved amount of norfloxacin suspension and of raw material at various times.

Time (min.)	Dissolved amount (%)[a]		p Value 2-tailed t Test
	Suspension	Raw material	
0	0	0	-
5	75.98±9.44	81.54±3.98	0.21
10	81.90±7.54	89.68±1.40	0.03
15	81.25±9.06	91.60±1.41	0.02
30	80.59±7.69	90.41±1.65	0.01
45	82.83±7.99	90.72±1.05	0.04
60	82.73±7.84	90.34±1.22	0.04

[a] Reported as mean±SD, n=6.

3.3 Chemical analysis

The concentration of the suspension should be 20 mg/ml when calculated based on the amounts of ingredients in the formula in Table 1. The experimental concentration was only 16.67±0.81 mg/ml or 83.35% of the theoretical concentration. This may be due to the quality of the drug raw material. However, the point we would like to study was the stability of the product. Therefore, the percentages of initial concentration remaining were calculated by comparing the drug concentrations at the observed times to the initial concentration. The results of the percentages of initial concentration remaining are presented in Table 3. The range of 94.71% and 100.56% of the mean initial norfloxacin concentration remained at ambient temperature. Assuming that drug concentrations equal to or greater than 90% of the initial value indicate stability, the results indicate that the suspension, stored in amber glass bottles at ambient temperature, was chemically stable for 85 days. It was found that percentages of drug remaining at 40°C were higher than 100%. This may be because of the loss of aqueous medium while storing in the hot air oven. The stability at 40°C could not be concluded because the humidity could not be controlled at 75%RH. The data, however, showed variability to some extent since the heterogeneous property of the suspension may cause an error in taking samples and day-to-day variation may also cause the deviations.

Table 3 Results of stability studies.

Temperature	Initial Concentration Remaining[a] (%)		
	Day 28	Day 56	Day 85
Ambient Temperature (28±2°C)	99.62±7.63	94.71±4.43	100.56±3.64
40°C	106.52±5.81	111.31±8.97	-

[a] Reported as mean±SD, n=6 and based on 100% on Day Zero.

4. Conclusion

In summary, this investigation has shown that the formula proposed in Table 1 can be used in norfloxacin suspension preparation. The product had acceptable physical properties and the ingredients used in the formula did not affect chemical stability of the drug under the studied conditions. However, this investigation just suggests that the studied formula can be used, deeper data about stability and safety should be further studied.

5. Acknowledgment

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6. References

[1] Mazuel, C., Norfloxain, In: Florey, K. (Ed.): Analytical Profiles of Drug Substances, Academic, San Diego, CA, Vol.20, pp. 557-600, 1991.

[2] Sifton, D.W., Physicians Reference (PDR), 49th ed., Medical Economics, New York, pp. 1600-1602, 1998.

[3] Hor, H., MIMS, Medi Media, Vol.27, No.1, pp. 204-210, 1998.

[4] Buduvari, S., The Merck Index, 12th ed., Merck and Company, Rahway, NJ, p. 1150, 1996.

[5] Ansel, H.C., Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea and Febiger, Philadelphia, PA, pp. 207-222, 1985.

[6] Nairn, J.G., Solutions, Emulsions, Suspensions and Extracts, In: Gennaro, A.R. (Ed.): Remington: the Science and Practice of Pharmacy, 19th ed., Mack Publishing, Easton, PA, pp. 1515-1521, 1995.

[7] Boonme, P., et al. Stability of Extemporaneous Norfloxacin Suspension, Drug Dev. Ind. Pharm., Vol.26, No.7, pp. 777-779, 2000.

[8] Martin, A., Physical Pharmacy, 4th ed., Lea and Febiger, Philadelphia, PA, pp. 453-467, 1993.

[9] Cardenas, R.H.L., et al. Investi-gation of Dissolution Profiles from Suspensions Containing Benzoyl Metronidazole Using a statistical Model with Repeated Measurements, Drug Dev. Ind. Pharm., Vol. 20, No. 6, pp. 1063-1073, 1994.

[10] United States Pharmacopeial Convention, Inc., The United States Pharmacopeia, 23rd rev., Rockville, MD, pp.1103-1104, 1995.

[11] Nangia, A., Lam, F., Hung, C.T., A Stability Study of Aqueous Solution of Norfloxacin, Drug Dev. Ind. Pharm., Vol.17, No.5, pp. 681-694, 1991.